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CAN THE NEUROLOGIC COMPLICATIONS OF PERNICIOUS ANEMIA BE PREVENTED?

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Nine years has elapsed since Minot and Murphy discovered the value of liver therapy for pernicious anemia. This period of time appears sufficiently long to allow a fair evaluation of the results achieved. But while this may hold true for the hematologic phase of the disease, there is considerable diversity of opinion concerning the neurologic aspects. This relates to two distinct questions: one is whether neurologic complications, once they have arisen, can be ameliorated or made to disappear by means of liver therapy; the other is whether adequate therapy can prevent the onset of neurologic complications in a patient not as yet affected.

In a previous study [1] I reported some observations bearing on the first problem. The findings indicated that in cases of advanced subacute combined degeneration treatment with liver had negligible effects. These findings appeared in conformity with what one would anticipate from a knowledge of the underlying pathologic condition in this stage of the disease—an irreparable destruction of the axis-cylinders. At the same time mention was made of the more auspicious reports of other investigators, for instance, Ungley and Suzman, Minot and Murphy and Richardson, and it was suggested that perhaps the earlier and more intensive application of treatment, at a time when irreversible changes in the nervous system had not yet occurred, accounted for the favorable results obtained.

The present study is concerned with the second question mentioned, namely, whether the neurologic complications of pernicious anemia can be prevented. The material for the previous study, coming as it did from the wards of a service for patients with chronic nervous diseases, could not be utilized for this purpose, since, obviously, only patients who already showed neurologic complications severe enough for them to seek hospitalization would be available. The opportunity to study a

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1. Needles, W.: Neurologic Complications of Pernicious Anemia, Arch. Neurol. & Psychiat. **26**:346 (Aug.) 1931.

more suitable group was offered in the hematologic clinic of the Mount Sinai Hospital, where patients with earlier stages of the disease were encountered.[2] There 30 consecutive and unselected cases of pernicious anemia were studied. Some of these cases had to be excluded from consideration because of the presence of other etiologic factors capable of producing changes in the nervous system. Thus, one patient had syphilis, another had shown neurologic signs immediately after the intraspinal injection of an anesthetic and a third had, in addition to anemia, diabetes mellitus, chronic alcoholism and hypertension.

Another group of cases had to be eliminated because the liver therapy was inadequate, in some instances because the patient wilfully neglected the prescribed regimen (5 cases) or because what seemed to be an adequate and carefully supervised administration of liver did not produce the desired result, judging by the hematopoietic response (2 cases). One of these patients had to be readmitted to the hospital, and there signs of severe anemia were presented. The other, though receiving maintenance doses of liver, repeatedly showed an unsatisfactory hemoglobin content, ranging from 49 to 65 per cent.

In still another group of cases which were considered unsuitable there was evidence of neurologic involvement prior to the time when liver therapy was instituted (4 cases).

Finally, 2 cases in which signs of mild involvement of the spinal cord were present were not included, since they had not, before the beginning of therapy, been subjected to a detailed neurologic examination and preexistent neurologic signs had not been ruled out. This may well happen if the patient is observed in the medical ward of a hospital, as usually happens, and does not present striking evidence of neurologic disease. The more subtle deviations from the normal may then be overlooked.

It is apparent that a considerable proportion of the cases originally studied had to be discarded. But the criteria for exclusion cannot be regarded as too rigid if one agrees that in evaluating the effects of liver therapy one should deal with (1) patients whose neurologic status has been carefully checked before the institution of therapy and who have been found normal, (2) patients who are free from other conditions capable of producing neurologic signs and (3) patients who have faithfully adhered to the treatment and have received adequate doses of liver, as determined by the response of the blood. Actually, consistent adherence to these criteria would have diminished the number of cases even more.

Certain difficulties, which have doubtless confronted other investigators in this field, were encountered in the study of these cases. Owing to the prolongation of life happily afforded by the use of liver, the

2. Dr. Nathan Rosenthal gave permission for the study of these cases.

history has in many cases become a long one. The patients as a result are often uncertain and hazy about the vicissitudes of treatment, especially when the doses, the preparation and the route of administration have varied from time to time. For this reason also the treatment of one patient cannot readily be compared with that of another.

In addition, there is always the human factor to be dealt with, often thwarting the most assiduous attempts at accuracy. This was brought out strikingly, for example, in a patient who, despite apparently adequate therapy, had shown progression of the neurologic signs. When this patient, a rather proud and independent person, was questioned more closely, she admitted somewhat reluctantly that she had accepted the prescription for liver extract each time but that, not having the money to pay for the drug and not wishing to disclose her poverty, she had gone home without having the prescription filled. The records of the clinic indicated simply that the patient was receiving therapy regularly.

Another difficulty arises from the fact that since the disease not infrequently affects persons of advanced age, there may supervene, during the course of treatment, manifestations of neurologic disease not necessarily attributable to subacute combined degeneration. Arteriosclerotic changes may play a rôle, or the patient may manifest the "normal" alterations, notably of vibratory sensation, that the studies of Weisenburg have made familiar.

Cognizance has been taken of these various facts, and an attempt has been made to give them due consideration wherever necessary.

COMMENT

Of the 13 patients studied, the first showed minimal evidence of neurologic involvement eight and one-half years after the onset of symptoms, the second showed no involvement after eight and one-half years, the sixth showed no involvement after five and one-half years, the ninth showed no involvement after four and one-half years and the tenth showed no involvement after five and one-half years. The third patient showed slight signs of involvement of the pyramidal tracts seven and one-half years after the onset of the illness. The fourth patient, in whom the disease had run for nine years, showed merely vibratory disturbances over the lower half of the body. In both the last 2 cases there was no record of a detailed neurologic examination before liver therapy was instituted for purposes of comparison with the recent status. The fifth patient six years after the onset presented vibratory disturbances in the lower half of the body and moderate hyperreflexia. In view of the age of the patient and the presence of marked generalized vascular disease, even the few signs presented could not be attributed entirely to subacute combined degeneration. The seventh patient showed moderate hyperreflexia, a positive Babinski sign on

the left side, vibratory disturbances in the lower half of the body and disturbances of the position sense in the small toes of both feet six years after the onset of symptoms. However, the liver therapy was

Data on Thirteen Patients with Pernicious Anemia

Case	Duration of Symptoms Before Institution of Treatment	Duration of Treatment, Years	Neurologic Status Before Institution of Treatment	Present Neurologic Status	Comment
1	12 mo.	8½	Normal	Hyperactive knee jerks; diminished vibration at toes	
2	Short time (indefinite)	8½	Depression of deep reflexes	Normal	Brief omission of therapy
3	6 mo.	7½	Detailed information lacking	Slight signs of involvement of pyramidal tracts	
4	8 mo.	9	Detailed information lacking	Vibratory disturbances at and below iliac crests	
5	?	6	Detailed information lacking	Vibratory disturbances at and below iliac crests; moderate hyperreflexia	Aged 67; vascular disease
6	6 wk.	5½	Normal	Normal	Brief omission of therapy
7	2 mo.	6	Normal	Moderate hyperreflexia; Babinski sign on left; vibration diminished at and below iliac crests; loss of position sense at toes	Inadequate therapy; aged 66
8	?	4½	Normal	Vibration sense absent in left foot; diminished in right foot and fingers	
9	6 mo.	4½	Detailed information lacking	Normal	Therapy inadequate at times
10	12 mo.	5½	Normal	Normal	Occasional lapses of therapy
11	6 mo.	4	Detailed information lacking	Minimal vibratory disturbances; hyperactive knee jerks	Aged 59; inadequate therapy at times
12	18 mo.	6½	Weakness of legs; loss of vibration sense at and below ilium	Hyperreflexia; vibration as before; loss of position sense in toes	
13	2 yr.	8½	Upper reflexes diminished; loss of ankle and knee jerks; ataxia of upper limbs; vibratory disturbances	Reflexes of upper extremities depressed; vibration sense disturbed in all limbs	

not optimal in this case. The eighth patient showed merely vibratory disturbances in the hands and feet after at least four and one-half years of illness. The eleventh patient after four years of illness showed minimal vibratory disturbances in the hands and feet and hyperactive patellar and suprapatellar reflexes. However in a person aged 59 these findings are not so definitely indicative of subacute combined degenera-

tion as they would be in a younger person. In addition, lapses of therapy occurred in this case. The last 2 patients, who presented some evidence of neurologic involvement before they were given liver therapy six and one-half and eight and one-half years, respectively, after the onset of symptoms, showed no significant progression of the involvement.

The salient features in these 13 cases are shown in the accompanying table.

One fact that stands out significantly in this study is the relatively short period for which each patient was ill before the diagnosis of pernicious anemia was established and appropriate therapy was instituted, and brings out clearly the necessity for early diagnosis and treatment.

When one considers the usual course of pernicious anemia and subacute combined degeneration before liver therapy was introduced, the results obtained at present can be better appreciated. Even after the development of paresthesias in the limbs has been ruled out as sufficient evidence of involvement of the spinal cord, estimates of the frequency of disease of the spinal cord in pernicious anemia vary from 40 per cent (Suzman) to 80 per cent (Woltman). Cabot reported lesions of the spinal cord in 84 per cent (82 cases) of those examined histologically. Presumably, the longer the illness lasts before treatment is instituted, the greater the probability that spinal complications will supervene, so that in a group of patients with such an unusually long duration of symptoms as was noted here the incidence of involvement of the spinal cord would have been high. Yet, some of these patients have already been ill for from four to eight and one-half years without any evidence of involvement of the spinal cord, and some have been ill for an equal period of time with only minimal or mild involvement. The average duration of the illness for the patients who are still alive and well is six and one-half years, a period exceeding by far not merely the time usually required for the development of a severe pathologic condition of the spinal cord but the customary duration of the entire illness before the advent of liver therapy. For, according to Cabot,[3] in his study based on 1,200 cases of pernicious anemia, 556 of 699 deaths occurred within three years and 628 within four years.

It has been noted in several instances (cases 2, 6, 7, 9, 10 and 11) that therapy was not entirely satisfactory, either because the patient disregarded medical advice or because what was regarded as a maintenance dose of liver did not evoke a satisfactory response as judged by the blood picture. It may at first glance appear illogical, on the one hand,

3. Cabot, R. C., in Osler, W., and McCrae, T.: Modern Medicine, Philadelphia, Lea & Febiger, 1915, vol. 4.

to attribute the appearance of signs in one group of patients to the inadequacy of therapy and then to point out that some of the patients remained entirely or almost entirely free from neurologic complications despite lapses in therapy. This seeming paradox is resolved on closer analysis, however; for while one must agree that a patient who was not adequately treated and subsequently showed signs of involvement of the spinal cord might conceivably have shown a similar course with adequate therapy—such has been the experience of numerous observers, as well as mine—nevertheless there is no justification for assuming that this is true in all cases. The present study illustrates this. On the other hand, as regards the patients who fared well despite certain lapses in therapy, one must conclude that the amount of liver which these patients received was adequate to tide them over the periods when they abstained from liver. It cannot be denied that without liver therapy these patients would have shown imposing signs of myelopathy and would have succumbed in a much shorter time than they have survived, neurologically intact, thus far. The impression is gained that there is variability in the individual resistance to disease of the spinal cord and that one person may require a smaller maintenance dose of liver than another to keep the nervous system intact.

In the literature one finds as little unanimity of opinion regarding the preventive value of liver in subacute combined degeneration of the spinal cord as one does regarding its curative value, once signs of involvement of the spinal cord have set in. In the previous study the divergent views of Minot and Murphy, Lottig, and Witzleben and Ungley and Suzman, on the one hand, and of Curschmann and Redlich, on the other, were cited. Reference to more recent studies shows that this divergence of opinion still exists. Thus, Starr [4] reported on 8 cases of pernicious anemia. In 4 patients who were considered to have received adequate treatment, there was no progression in the neurologic signs, but in 4 who were considered to have received inadequate treatment, 2 of whom had serious infection of the bladder, such progression did occur. Christoffersen [5] reported on 24 patients with pernicious anemia who were treated for from one to four years. Twelve of these patients remained free from neurologic involvement. Four showed evidence of neurologic involvement before therapy was instituted. Of the 8 patients in whom signs developed during the course of treatment, only 1 was considered as having been adequately treated. Meulengracht [6] reported on 17 patients who showed improvement after liver

4. Starr, P.: The Prevention of Spinal Cord Degeneration in Pernicious Anemia, J. A. M. A. **96**:1219 (April 11) 1931.

5. Christoffersen, N. R.: Anämische Myelopathien bei Leberbehandlung, Acta med. Scandinav., supp. 50, 1932, p. 395.

6. Meulengracht, E.: Verhütung und Behandlung der Rückenmarksstörungen bei perniziöser Anämie, Klin. Wchnschr. **12**:1163 (July 29) 1933.

extract was replaced by stomach preparations. He expressed the opinion that most of the patients in whom myelopathy developed after treatment had been instituted were doubtless underdosed, since they improved when stomach preparations were substituted. In a discussion before the Royal Society of Medicine Witts [7] mentioned the experiences of Wilkinson, who treated 264 patients with pernicious anemia for periods ranging up to three and one-half years without the development of neurologic signs. All were treated with preparations of stomach orally. Seyderhelm,[8] on the other hand, reported that of 53 patients who died of pernicious anemia, signs of involvement of the spinal cord developed in 7 despite therapy; of 40 living patients, 4 showed the development of signs despite therapy. He found that the patients who escaped spinal complications were those who showed especially high red blood cell counts during remissions. Garvey, Levin and Guller [9] found that of 19 patients who originally showed no neurologic involvement, 9 had been satisfactorily treated, and in only 1 did signs of involvement of the spinal cord develop; while of 10 unsatisfactorily treated patients, 5 became neurologically affected. Grinker and Kandel [10] studied a fairly large series of cases and concluded that "liver therapy is not efficacious in improving or preventing degeneration in the central nervous system complicating pernicious anemia." Analysis of their cases, however, shows that only 2 patients (cases 20 and 27) were neurologically intact before treatment was instituted and that signs developed subsequent to treatment. There is little ground, therefore, for their generalization as to the preventive value of liver therapy. Finally, Goldhamer, Bethell, Isaacs and Sturgis,[11] in their series of 461 patients, found 18 who were neurologically normal at the original examination. In 8 of these patients spinal complications developed, while in 9 they did not. One patient could not be followed.

In the light of these facts it is obvious that at present it is impossible to formulate any hard and fast rule regarding the preventive value of liver. In some cases liver therapy prevents the onset of myelopathy; in others it does not.

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7. Witts, L. J., in Discussion on the Treatment of Subacute Combined Degeneration, Proc. Roy. Soc. Med. **27**:787 (April) 1934.

8. Seyderhelm, R.: Sieben Jahre Lebertherapie, Deutsche med. Wchnschr. **59**:1193 (Aug. 4) 1933.

9. Garvey, P. H.; Levin, P. M., and Guller, E. I.: Effect of Liver Therapy on the Neurologic Aspects of Pernicious Anemia, Ann. Int. Med. **6**:1441, 1933.

10. Grinker, R. R., and Kandel, E.: Pernicious Anemia: Results of Treatment of the Neurologic Complications, Arch. Int. Med. **54**:851 (Dec.) 1934.

11. Goldhamer, S. M.; Bethell, F. H.; Isaacs, R., and Sturgis, C. C.: The Occurrence and Treatment of Neurologic Changes in Pernicious Anemia, J. A. M. A. **103**:1663 (Dec. 1) 1934.

Of the patients who formed the basis for this study, it so happened that none who received sufficient treatment showed more than insignificant neurologic signs—and then, in several cases not definitely attributable to subacute combined degeneration—while 4 showed no signs whatever. The cases were thought to be especially informative because of the long duration of the illness. The reason for the different responses in different patients is still unknown. It may ultimately be found to rest on variations in the constitutional make-up. Before this impression is established as a fact, however, it will be necessary to study a large group of patients at approximately the same stage of the disease and treated with equal doses of the same preparation of liver. In other words, it will be necessary to rule out the possibility that one type of preparation may be more potent than another in combating the myelopathic process in pernicious anemia.

The present series of cases, at any rate, renders one a little more optimistic about the chances of obtaining gratifying results and indicates that the attitude of therapeutic nihilism that exists in certain quarters is not justified. The development of subacute combined degeneration certainly must not be regarded as inevitable. If any added stimulus is needed at this late date for prompt and energetic treatment of pernicious anemia, the present findings provide it.

The detailed report of the cases is given in the reprints of this article.

POSTURAL HYPOTENSION

WITH PARTICULAR REFERENCE TO ITS OCCURRENCE IN DISEASE OF THE CENTRAL NERVOUS SYSTEM

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Normally, the arterial blood pressure in man is maintained relatively stable in spite of marked variations in body posture. Failure of this postural adaptation occasionally occurs, with the production of symptoms which may handicap the patient severely. Bradbury and Eggleston [1] first described the clinical syndrome of "postural hypotension" in 1925. Since that time a total of twenty-six definite case reports have appeared in the literature,[2] including reports of cases in which the hypotension

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1. Bradbury, S., and Eggleston, C.: Postural Hypotension: A Report of Three Cases, Am. Heart J. **1**:73, 1925.

2. (*a*) Ghrist, D. G., and Brown, G. E.: Postural Hypotension with Syncope: Its Successful Treatment with Ephedrin, Am. J. M. Sc. **175**:336, 1928. (*b*) Asworth, O. O.: Postural Hypotension: A Report of Two Cases, Virgina M. Monthly **56**:260, 1929. (*c*) Riecker, H. H., and Upjohn, E. G.: Postural Hypotension, Am. Heart J. **6**:225, 1930. (*d*) Schellong, F.: Störung der Kreislaufregulation, eine neues Symptom bei Insuffizienz des Hypophysenvorderlappens, Klin. Wchnschr. **10**:100, 1931. (*e*) Strisower, R.: Ueber bedeutende Blutdrucksenkung nach Arbeit und bei Aenderung der Körperlage bei Tabes dorsalis, Ztschr. f. klin. Med. **117**:384, 1931. (*f*) Barker, N. W., and Coleman, J. H.: Postural Hypotension Associated with Arteriosclerosis, M. Clin. North America **15**:241, 1931. (*g*) Sanders, A. O.: Postural Hypotension: A Case Report, Am. J. M. Sc. **182**:217, 1931. (*h*) Duggan, L. B., and Barr, D. P.: Postural Hypotension Occurring in a Negro with Addison's Disease, Endocrinology **15**:531, 1931. (*i*) Laubry, C., and Doumer, E.: L'hypotension orthostatique, Presse méd. **40**:17, 1932. (*j*) Sanders, A. O.: Postural Hypotension with Tachycardia: A Case Report, Am. Heart J. **7**:808, 1932. (*k*) Lian, C., and Blondel, A.: L'hypotension artérielle orthostatique, Paris méd. **1**:179, 1933. (*l*) Barker, N. W.: Postural Hypotension: Report of a Case and Review of the Literature, M. Clin. North America **16**:1301, 1933. (*m*) Allen, E. V., and Magee, H. R.: Orthostatic (Postural) Hypotension with Syncope, ibid. **18**:585, 1934. (*n*) Gainshorn, J. A., and Horton, B. J.: Postural Hypotension: Report of a Case, Proc. Staff Meet., Mayo Clin. **9**:541, 1934. (*o*) Weis, C. R.: Postural Hypotension with Syncope: Report of a Case Cured with Ephedrine Sulfate, Ann. Int. Med. **8**:920, 1935. (*p*) Croll, W. F.; Duthrie, R. J., and MacWilliam, J. A.: Postural Hypotension: Report of a Case, Lancet **1**:194 (Jan. 26) 1935.

occurred in association with tabes dorsalis and Addison's disease. It is questionable whether certain additional cases reported should be included in the total number. Schellong [2d] cited five cases of postural hypotension but gave insufficient data on three to warrant their inclusion. In two of the cases reported by Laubry and Doumer [21] (cases 3 and 5) the fall in blood pressure was so slight, inconstant and transitory that, as Barker [21] suggested, it seems unjustifiable to class these cases among those of this syndrome. The same objection holds for the cases reported by Tripodi [3] and by Rudsit.[4] It therefore appears that this condition is either of rare occurrence or is relatively seldom recognized. It is our belief that it is not uncommon, although patients with severe and dramatic symptoms are probably not frequently encountered. In the past two and one-half years we have seen six patients with postural hypotension at the Boston City Hospital.

In their original description of postural hypotension Bradbury and Eggleston [1] tabulated seven characteristics of the condition. These were (1) a syncopal attack when the patient stood, with a marked drop in the systolic blood pressure, (2) a slow and unchanging pulse rate, (3) anhidrosis, (4) increased distress during the heat of summer, (5) a slightly low basal metabolic rate, (6) signs of slight and indefinite changes in the central nervous system and (7) a blood urea content at the upper limit of normal. In addition, they frequently encountered (1) a greater output of urine at night than during the day, (2) impotence, (3) a false appearance of youth, (4) pallor and (5) secondary anemia. In the cases cited in subsequent reports all of these characteristics have not been shown, which is not surprising since the original report was based on an analysis of only three cases. It now appears justifiable to define the syndrome of postural hypotension, as has Barker,[21] as one in which there is an immediate, persistent and marked fall in the systolic blood pressure when the patient stands and a similar but somewhat smaller drop in the diastolic blood pressure, frequently accompanied with dizziness, fainting and other symptoms. The drop in the systolic pressure in each case should be frequently but not necessarily invariably as great as 50 mm. of mercury. Partial or complete anhidrosis is of frequent occurrence. A heart rate which either is absolutely unchanged or fails to increase to a normal degree when the patient stands is also commonly seen, particularly in the cases of severe involvement.

The following report concerns the clinical observations made on six patients with postural hypotension, on two of whom a detailed physio-

3. Tripodi, M.: L'ipotensione arteriosa orthostatica, Policlinico (sez. prat.) **39**:797, 1932.

4. Rudsit, K.: Zur Behandlung vasoneurotischer Störungen mit Hypophysenvorderlappenpräparaten mit besonderer Rücksicht auf die Blutdruckreaktion bei Aenderung der Körperlage, Wien. klin. Wchnschr. **47**:878, 1934.

logic investigation was carried out concerning the mechanism of the disturbance.

CASE 1.—*Clinical History.*—H. H., a 57 year old married man, a locksmith, entered the neurologic service of the Boston City Hospital on July 22, 1932, complaining of weakness. For six months he had had generalized abdominal soreness which was relieved by pressure, anorexia, gas, alternating constipation and looseness of the bowels and impotence. He had lost 34 pounds (15.5 Kg.) in the past year. For four weeks he had suffered from increasing weakness and dizziness on standing. Twice he had fainted when getting out of bed.

The family, marital and past histories were noncontributory.

Physical Examination.—The patient was pale and had an anxious expression. He appeared older than his age and gave evidence of having lost weight. The legs showed marked varicose veins. There was no definitely abnormal pigmentation. Neurologic examination showed no pupillary abnormality; there was slight rotatory nystagmus on the left and some impairment of hearing. Postural hypotension was present, as will be discussed later.

Laboratory Findings.—Repeated examination of the urine showed the presence of albumin in amounts varying from moderate to large. The specific gravity was fixed at from 1.010 to 1.012. The centrifugated sediment showed an occasional leukocyte and granular cast. The blood was normal as to the hemoglobin and the number of red and white corpuscles. The Kahn test of the blood was negative. The nonprotein nitrogen content of the blood was normal, ranging about 30 mg. per hundred cubic centimeters until two days before the patient died, when it rose to 175 mg. The blood sugar content during fasting was 80 mg. No occult blood was present in the stool. Gastric analysis showed normal amounts of free hydrochloric acid after an alcohol test meal. Rentgenograms of the gastrointestinal tract gave negative results.

A diagnosis of postural hypotension was made, but no underlying organic disease could be demonstrated, with the exception of evidence of some renal damage. Addison's disease was seriously considered, but not enough confirmatory evidence existed to make the diagnosis definite.

Course.—Treatment was of no avail. Ephedrine in doses of ¾ grain (0.05 Gm.) three times daily, epinephrine and extract of adrenal cortex gave no relief. Atropine made the patient feel weaker.

The patient's condition gradually grew worse. The weakness increased, and attacks of syncope became more frequent. On November 14 slight fever developed for the first time. The patient became markedly weaker, but no new symptoms developed. He died quietly in his sleep on November 21.

Autopsy.—The relevant autopsy observations were as follows: The heart was essentially normal in size, weighing 380 Gm. The myocardium was pale and flabby. There was marked sclerosis of the coronary arteries, but the lumens of these vessels were everywhere patent. The aorta showed moderate atheromatous changes and scarring; there was slight atheroma of the cerebral vessels. The carotid sinuses, unfortunately, were not examined. The lungs showed chronic passive congestion and an early stage of bronchopneumonia. The adrenal glands were grossly normal, but microscopic examination revealed an extensive deposit of pink-staining hyaline material, chiefly in the middle zone of the cortex, with marked atrophy of the cellular elements due to pressure. There was moderate central congestion of the liver, with an acute hydropic degeneration of the center of the lobules and portal lymphocytic infiltration. The kidneys were

enlarged, weighing together 620 Gm. There was extensive destruction of the cortex, with infiltration by large numbers of leukocytes and the formation of multiple small abscesses. The glomeruli in the affected area were relatively well preserved. There was moderate hyalinization of small vessels. In the spleen there was a moderate amount of hyaline material, partly replacing the germinal centers. There was cerebral edema, but the brain was otherwise grossly and microscopically normal except for a cyst of the left choroid plexus, 2 by 1 by 1 cm. The spinal cord was not examined.

Pathologic Diagnosis.—The diagnosis was an early stage of bronchopneumonia and pulmonary edema, acute hydropic degeneration of the liver, infectious nephritis —due to Streptococcus haemolyticus and Bacillus coli-communis, amyloidosis of the adrenal glands and spleen, cerebral edema and cyst of the choroid plexus.

CASE 2.—*Clinical History.*—M. T., an American housewife aged 69, entered the Boston City Hospital on June 6, 1934, complaining of weakness and attacks of dizziness on standing which had been noted for nine months. The dizziness, which had been progressive, consisted essentially of an "all gone" feeling, with blurring of vision but no rotatory vertigo. The patient had never completely lost consciousness but had repeatedly been forced to lie down to prevent what she was sure would have been complete unconsciousness, and on several occasions she had actually collapsed. In a recumbent position she felt well.

For fourteen years she had suffered from diabetes mellitus, which was well controlled by diet and about 20 units of insulin daily.

For the past year the patient had not noticed any sweating, even in warm weather, and for about two and one-half years she had suffered from increasing paresthesia and some numbness of the lower portion of the legs and feet and to some extent of the hands. She had always been constipated.

The family, marital and past histories were noncontributory.

Physical Examination.—The patient was pallid and had a pasty complexion. She looked somewhat young for her age. The pupils were of normal size, equal and regular. They reacted to light and in accommodation. The heart was slightly enlarged, with a moderately loud systolic murmur, maximal in the pulmonic area, and an accentuated aortic second sound. The rhythm was regular at a rate of 72. The brachial and radial arteries were somewhat thickened. With the patient recumbent the arterial blood pressure was somewhat elevated, and there was postural hypotension. The lungs and abdomen were normal. There was moderate varicosity of the veins in both legs. Neurologic examination showed hyperactive but equal deep reflexes, except for the ankle jerks, which were absent. The vibration sense was absent in both legs, and the sense of position was slightly impaired in the feet.

Laboratory Findings.—The urine was normal except for an occasional trace of sugar. The red blood cell count was 4,700,000, and the hemoglobin value, 81 per cent. The stained smear showed normal red and white blood cells. There was complete gastric anacidity, even after the administration of histamine. The nonprotein nitrogen content was 34 mg. per hundred cubic centimeters of blood. The basal metabolic rate was minus 13 per cent. The Kahn test of the blood gave a negative result.

A diagnosis was made of diabetes mellitus, mild arterial hypertension, mild generalized arteriosclerosis, postural hypotension and possibly beginning combined system disease.

Course.—The course during the patient's stay in the hospital was uneventful. Her condition was extensively studied, as will be described later. She was dis-

charged on July 11. The dizziness was adequately controlled by 25 mg. of ephedrine sulfate by mouth three times daily, but the symptoms of weakness continued. She was given in addition ½ grain (0.03 Gm.) of thyroid daily and biweekly injections of 10 cc. of liver extract. On September 2 she suffered a mild attack of coronary thrombosis and reentered the hospital on September 9. Recovery was uneventful, and the patient was discharged on November 2. The condition has remained essentially unchanged.

CASE 3.—*Clinical History.*—P. P., a French-Canadian newspaperman aged 46 and single, had been followed by the neurologic service of the Boston City Hospital for four years. In 1925 he burned his right hand severely, apparently because of a loss of temperature sensation. Shortly thereafter he noticed diplopia, hoarseness and numbness and weakness of the right hand and arm and later of the left hand and both legs. The symptoms had progressed until about four years before the present studies were made, since which time there had been little change. For seven years he had had practically no sweating. Occasionally during the past three or four years he had noticed some dizziness and blurring of vision when erect, but this symptom had been intermittent and never severe, and there had been no fainting. Otherwise the history was unimportant.

Physical Examination.—With the exception of the neurologic findings and the postural hypotension, the results of physical examination were normal. The patient had a florid complexion even when erect. Neurologic examination on April 21, 1935, revealed rotatory nystagmus. The right pupil was larger than the left, and both pupils reacted poorly in accommodation but well to light. There was some hoarseness. Movement of the palate was diminished on the left, and the tongue was deviated to the left. The biceps reflex was absent on the right, and the radial and abdominal reflexes also were absent. The cremasteric reflex was diminished on the left. Bilateral Babinski and Chaddock reflexes were noted. There was absence of pain sensation over the face, and the temperature sense was absent over the head and shoulders as far as the level of the fifth cervical vertebra. There was a diminished sense of touch over the head and the lateral aspects of both arms. The sternocleidomastoid, trapezius and interosseus muscles were atrophied. There was slight weakness of both arms and the left leg and slight spasticity of the right leg. Past pointing and an intention tremor were noted in the right hand, with impairment of skilled actions. Bilateral adiadokokinesis, a tendency to fall toward the left and some ataxia were noted. A pilomotor test revealed no abnormality.

Laboratory Findings.—Examination of the urine and spinal fluid and the red and white blood cell counts gave normal results. The Kahn reaction of the blood gave a negative result. The basal metabolic rate was minus 10 per cent.

Diagnosis.—The diagnosis was syringomyelia and postural hypotension.

CASE 4.—*Clinical History.*—G. B., a single, unemployed Negro aged 69 years, was seen in the neurologic outpatient clinic of the Boston City Hospital on May 5, 1933, at which time a diagnosis of tabes was made. Lumbar puncture showed results consistent with an inactive lesion. The patient was unable to state the time of the appearance of the original syphilitic lesion. For ten years he had had lightning pains in the legs. There were no other tabetic symptoms. The patient had never perspired much and for the past eight or ten years practically not at all. Until two weeks before the studies were made, on July 31, 1934, he had never noticed dizziness; since then he had had several attacks while walking. There had been no gastro-intestinal disturbance or nocturia. Otherwise the history was irrelevant.

Physical Examination.—On July 31, 1934, examination revealed no abnormality except for the neurologic findings and evidence of postural hypotension. The patient looked young for his age. The pupils were small, irregular, slightly unequal and fixed to light and reacted sluggishly in accommodation. The knee and ankle jerks were absent, and the position and vibration senses in the legs were impaired.

Diagnosis.—The diagnosis was tabes dorsalis and postural hypotension.

CASE 5.—*Clinical History.*—M. L., a Jewish housewife aged 44, entered the Thorndike Ward of the Boston City Hospital on Nov. 27, 1934, with a complaint of nausea and vomiting for thirteen years. The gallbladder had been removed one year prior to the patient's present admission to the hospital, following which she was free from gastric symptoms for six months. Then the symptoms returned and were for the first time accompanied with cramps. For thirteen years she had been under treatment for tabes. For several years she had had shooting pains in the legs.

For a number of years she had been troubled with attacks of dizziness, which frequently continued until she fainted. These occurred when she assumed an upright position, usually in the morning. Lying down relieved the symptoms.

The family, marital and past histories were noncontributory.

Physical Examination.—The patient looked healthy. There was no abnormality except for the neurologic signs and postural hypotension. The pupils were small and irregular, the left one being smaller than the right. Both reacted in accommodation but not to light. The knee and ankle jerks were absent. Sensation to touch and the vibration sense were diminished in both legs and feet.

Laboratory Findings.—Examination of the urine and blood and roentgenograms of the gastro-intestinal tract revealed no abnormality. The Kahn reaction of the blood gave a weakly positive result. The spinal fluid showed 12 lymphocytes, a weakly positive Kahn reaction and a colloidal gold curve of 0011211000.

Diagnosis.—The diagnosis was tabes dorsalis, ? gastric crisis, ? gastric neurosis and postural hypotension.

CASE 6.—*Clinical History.*—R. H., an American clerk aged 32 years and single, was admitted to the neurologic service of the Boston City Hospital on April 22, 1934. He had fallen from a third story window onto the pavement. He was picked up unconscious and brought to the hospital. By the time of admission to the hospital he had regained consciousness but was in profound shock, from which he rallied somewhat in about four hours. His previous history was unimportant.

Physical Examination.—The abnormal physical findings were confined to the nervous system, with the exception of a few minor abrasions. There was complete loss of sensation from the level of the second dorsal segment down, and a partial sensory loss was noted in the first and second dorsal segments. The reflexes in the arm were present but much reduced. The patient could move the arms only slightly and suffered considerable pain in them. There was complete motor paralysis of the trunk and lower extremities, and the reflexes were absent.

Lumbar puncture showed no signs of block; the spinal fluid was slightly bloody. Roentgenograms of the spine revealed a fracture of the sixth cervical vertebra.

Course.—The reflexes of the lower extremities had returned by May 20, 1935, and a mass reflex was present. Automatic function of the bladder and anal sphincters was attained at the same time. Moderate sweating of the paralyzed part of the body and an increased pilomotor response also appeared. Decubitus

ulcers developed, but by June 1935 they were largely healed. The pain in the arms had disappeared, and the strength of the arms was increased somewhat. Otherwise he remained in essentially the same condition. By Dec. 25, 1934, however, there had been a slight return of sensation over the chest, and by June 2, 1935, he had slight sensory perception to the knees. The motor function remained entirely lost. After June 1934 he was able to sit in a reclining position at an angle of approximately 30 degrees in a wheel chair for two and one-half hours. There was some dizziness when he was first being propped up, but this gradually passed off. On some occasions, however, the dizziness was sufficiently marked to prevent his sitting at all. The vascular reactions were studied in June 1935.

Diagnosis.—The diagnosis was hematomyelia.

TABLE 1.—*Effect of an Erect Position and of Exercise on the Arterial Blood Pressure and on the Heart Rate*

	Arterial Blood Pressure, Mm. of Mercury			Heart Rate				
Case	Recumbent, Average and Range	Erect, Average and Range	Change Immediately After Exercise	Recumbent, Average and Range	Erect, Average and Range	Change Immediately After Exercise	Symptoms When Erect	Etiology
1	120/84	65/52	+10/+10	86	92	....	Feeling of faintness to absolute syncope	? ?? Addison's disease
2	154/80 110-190/60-100	91/62 62-135/46-86	−22/−16	73 70-84	75 75-86	+17	Dizziness; blurring of vision; "all gone" feeling	?
3	121/82 96-136/64-90	58/44 33-80/26-60	+42/+24	68 62-80	82 72-90	−6	Dizziness; buzzing in ears; blurring of vision	Syringomyelia
4	129/60 115-140/60-78	81/48 62-110/41-56	+32/+8	75 70-80	83 82-86	+12	Occasional dizziness	Tabes dorsalis
5	125/81 120-135/76-85	82/60 75-95/56-65	+2/0	104 100-110	110 106-114	0	Occasional dizziness	Tabes dorsalis
6	86-68	56/44	.....	95	105	..	Marked dizziness*	Hematomyelia
	98/74	42/30	.....	70	103	..	Marked dizziness†	

* Aug. 20, 1934, tilted to 40 degrees only.
† July 1, 1935, tilted to 60 degrees only.

INVESTIGATIVE PROCEDURES

Postural Hypotension.—Each patient showed an immediate, profound and persistent drop in the arterial blood pressure when in the erect position (table 1). The extent of the drop varied from time to time, frequently without detectable cause, although it was often worse on warm days. A marked drop was observed with least regularity in case 5, although on several occasions it exceeded 50 mm. of mercury. The drop in the blood pressure was the same whether the change of position was effected passively on a tilting table or actively by having

the patient stand. The development of dizziness in a given patient bore a rough relationship to the level of the blood pressure when he was erect, although this relationship was neither exact nor consistent. There was no correlation among the patients as to the level at which the symptoms developed.

The second patient showed no significant change in the heart rate when she stood. The fifth patient persistently had a pulse rate of from 100 to 120 regardless of her position. The remaining patients showed a rise in the heart rate when they stood, but it was less than one would expect as a compensation for the lowered blood pressure.

Exercise.—It has been noted previously [5] in cases of postural hypotension that immediately after a walking exercise the blood pressure may decrease and the patient's symptoms may increase. This was found to be true in case 2 but not in cases 1, 3, 4 and 5 (table 1). Schellong [2d] has also observed that exercise of the legs when the patient is recumbent produces a lowering of the arterial pressure. We were unable to confirm this observation in the three patients studied in this regard (cases 2 to 4), all of whom showed a slight rise in pressure.

Emotion.—It was noted that the patients, particularly the second patient, tended to show considerable fluctuations in blood pressure from day to day and that in cases 2 to 5 the blood pressure apparently rose under emotional stress. Unfortunately, the vascular reflexes of the first patient were not tested.

Pain.—In case 3 the application of an uncomfortably tight pressure cuff to the arm on one occasion produced an increase in the blood pressure with the patient recumbent and a lessening of the drop when the patient stood, but when the test was repeated there was no effect. Cuffs about the ankles, similarly, were without effect. In cases 2 and 4 no change was produced by tight cuffs about the arm.

It has been shown [6] that normally a sensory stimulus, such as pinching the skin of the arm, produces a definite and immediate decrease in the blood flow through that extremity. In the second patient, this reaction was entirely absent, although in the third patient it was normal. In the sixth patient the reaction was present, although its onset was delayed. The so-called galvanic reflex is a decrease of the cutaneous resistance, which also occurs as a result of a stimulus such as pinching.[7] This was normal in the third patient but absent in the second and sixth patients. It is of interest that it was absent in the patient with

5. Schellong.[2d] Strisower.[2e]

6. Capps, R. B.: To be published.

7. Solomon, P.: The Psychogalvanic Reflex: Applications to Neurology and Psychiatry, Arch. Neurol. & Psychiat. **34**:818 (Oct.) 1935.

transection of the spinal cord, since it has been shown [8] that in animals with experimental transection of the spinal cord, although there is a latent period of weeks during which the reflex is absent, it eventually returns.

Reflex Vasodilatation to Heat.—In cases 2 and 3 the blood flow in the hand was measured after one leg had been heated. Normal reflex vasodilatation was produced by this method in both patients. This test corresponds to that described by Gibbon and Landis,[9] who found that a reflex rise in the temperature of the skin was due to sympathetic impulses arising in the brain as a result of the stimulus of the warmed blood. In case 3 the effect of a change in posture was studied after one arm had been immersed in water at a temperature of 42 C. It was found that the drop in pressure and dizziness with the patient erect were greater than during a control observation.

Cold.—Immersion of the arm of this patient in ice-water increased the blood pressure with the patient recumbent from 100 systolic and 65 diastolic to 120 systolic and 80 diastolic, but it was without effect in lessening the drop when he stood. Gainshorn and Horton [2n] found in studying one patient with orthostatic hypotension by this procedure that the pressure was increased with the patient recumbent and did not fall to as low a level when he was standing.

TABLE 2.—*Effect of Pressure on the Carotid Sinus*

Case	Fall in Blood Pressure, Mm. of Mercury	Fall in Pulse Rate	Symptoms
1	6	0	0
2	10-42	Slight	0
3	0	0	0
4	20-25	0	0
5	14-54	Very slight	Dizziness
6	0	Slight	Slight dizziness

It is therefore apparent that the vascular reactions and certain at least of the vasomotor reflexes were maintained in the patients studied.

Carotid Sinus Reflex.—This reflex was studied in all patients, and the results are shown in table 2.

The fifth patient had a mildly hyperactive carotid sinus reaction, and the others had normal reactions. In only one, the patient with syringomyelia, was no effect produced. The two patients (cases 2 and 3) to whom sodium cyanide was administered intravenously for mea-

8. Richter, C. P.: Galvanic Skin Reflex from Animals with Complete Transection of the Spinal Cord, Am. J. Physiol. **93**:468, 1930.

9. Gibbon, J. H., Jr., and Landis, E. M.: Vasodilatation in the Lower Extremities in Response to Immersing the Forearms in Warm Water, J. Clin. Investigation **11**:1019, 1932.

surement of the circulatory time showed a normal respiratory response to the drug. It is known that sodium cyanide acts on the carotid sinus.[10] This is the only evidence available that the carotid sinuses of patients with postural hypotension react normally to internal stimulation.

Restriction of the Circulation to the Legs.—The effect of eliminating the circulation through the legs was studied in cases 2 to 4 by means of blood pressure cuffs around both thighs inflated until there was a pressure of 250 mm. of mercury.

In each case the drop in pressure was partially abolished. This was largly, if not entirely, due to the mechanical exclusion of the circulation in the legs, which removed an appreciable portion of the vascular bed involved in the disturbance in the postural reflex. That it was not caused by a vasoconstricting reflex resulting from the discomfort of the cuff on the thighs is indicated by the fact that cuffs around the ankles or one arm, with the one exception previously discussed, which were equally uncomfortable, failed to prevent the full

TABLE 3.—*Effect of Occluding the Circulation to the Legs*

Case	Blood Pressure, Recumbent		Blood Pressure, Erect		Symptoms, Erect	
	Without Cuff	With Cuff	Without Cuff	With Cuff	Without Cuff	With Cuff
2	148/80	156/84	60/50	90/62	Dizziness	0
3	118/80	134/96	66/46	114/84	Dizziness	0
4	126/70	124/70	88/56	110/61	0	0

drop in blood pressure, regardless of whether the blood pressure with the patient recumbent was somewhat elevated by the procedure.

These observations are in agreement with those of Allen and Magee [2m] but not with those of Ghrist and Brown,[2a] who noted no effect from this procedure. Our observations indicate that disturbance of the normal postural reflex is widespread, including the vessels of the lower extremities as well as those of the splanchnic area.

In case 1 tight bandaging of the legs reduced the dizziness when the patient stood, although it did not significantly change the drop in blood pressure. A similar effect in one case was observed by Bradbury and Eggleston.[1]

Effect of an Abdominal Binder.—The application of a tight abdominal binder also was effective in lessening the drop in blood pressure and the amount of dizziness in two of three patients.

10. Heymans, C.; Bouckaert, J. J., and Dautrebande, L.: Sinus carotidien et réflexes respiratoires: III. Sensibilité des sinus carotidiens aux substances chimiques; action stimulante respiratoire réflexe du sulfure de sodium, du cyanure de potassium, de la nicotine et de la lobéline, Arch. internat. de pharmacodyn. et de thérap. **40**:54, 1931.

Dynamics of the Circulation (Table 5).—Physiologic measurements of the hemodynamics were carried out with the subject on a tilting table, first recumbent and again after having been tilted to an angle of 75 degrees for at least ten minutes. The total blood flow was well maintained with the subject in the erect position. The decreases in cardiac output which were noted were no greater than those that are frequently found in normal subjects by the same method, particularly in those with poor postural adaptation.[11] Lian and Blondel [2k] found an increase in the cardiac output of one patient from 4 liters a minute recumbent to 12 liters when erect, a change which they attributed to increased muscular activity when he was erect. Since they gave no details regarding the method employed, this extraordinary finding can hardly be accepted. As regards the circulation time, Bock, Dill and Edwards,[12] using the histamine method, found the arm to face time of normal subjects essentially the same in the standing as in the lying position. Schellong and Heinemeier [11b] found that in patients with good adaptation the circulation time

TABLE 4.—*Effect of an Abdominal Binder*

Case	Blood Pressure, Recumbent		Blood Pressure, Standing		Symptoms, Erect	
	Without Binder	With Binder	Without Binder	With Binder	Without Binder	With Binder
1.....	.....	.....	46/40	46/40	Dizziness	Dizziness
2.....	144/85	144/86	84/56	102/66	Dizziness	0
3.....	124/85	126/83	56/40	85/40	Dizziness	0

by the calcium chloride method was essentially unchanged but that in those unable to maintain adequate postural adaptation it tended to be slowed. The changes in the circulation time which we found were comparable with the change in cardiac output and did not suggest a marked decrease in the blood flow. The femoral arteriovenous oxygen differences may be considered an index of the blood flow through the legs; i. e., as the oxygen difference decreases the blood flow increases. Normally, the arteriovenous difference increases markedly when a change is made from the recumbent to the erect position.[13] The changes

11. (*a*) Grollman, A.: The Effect of Posture on the Output of the Human Heart, Am. J. Physiol. **86**:285, 1928. (*b*) Schellong, F., and Heinemeier, M.: Ueber die Kreislaufregulation in aufrechter Körperstellung und ihre Störungen, Ztschr. f. d. ges. exper. Med. **89**:49 and 61, 1933. (*c*) Schneider, E. C., and Crampton, C. B.: The Effect of Posture on the Minute Volume of the Heart, Am. J. Physiol. **110**:14, 1934.

12. Bock, A. V.; Dill, D. B., and Edwards, H. T.: On the Relation of Changes in Blood Velocity and Volume Flow of Blood to Change of Posture, J. Clin. Investigation **8**:535, 1930.

13. Florkin, M.; Edwards, H. T., and Dill, D. B.: Oxygen Utilization in the Legs of Normal Men: I. Effect of Posture, Am. J. Physiol. **94**:459, 1930.

found in cases 2 and 3 were within the range of normal. Recent work on the effect of posture on the venous pressure [14] indicates that it is essentially unchanged. Formerly it was thought that the venous pressure tends to rise when the erect position is assumed.[15] McIntire and Turner [14] have emphasized the necessity of putting a support behind the subject's shoulders. The present studies were performed without a support, and the results may be considered within normal limits. Lian and Blondel [2k] found the same changes in venous pressure in a subject with postural hypotension as those obtained in normal subjects. It is

TABLE 5.—*Circulatory Measurements on Patients with Postural Hypotension*

Case	Position	Average Blood Pressure, Mm. of Mercury	Average Heart Rate	Oxygen Consumption, Cc. per Min.	Cardiac Output,* Liters per Min.	Arteriovenous Oxygen Difference in Leg, Vol. %	Circulation Time,† Arm to Head, Seconds	Venous Pressure in Arm,‡ Cm. of Water	Blood Volume,§ % of Body Weight
1	Horizontal	120/84	86	...	....	....	....	8	....
	Vertical	65/52	92	...	....	....	....	12	....
2	Horizontal	154/80	73	183	{2.60 {3.12	7.17	19.5	4	....
	Vertical	91/62	75	234	{2.83 {2.10	10.36	24	10	....
				232	{2.65 {2.64				
3	Horizontal	121/82	68	218	{3.70 {3.46	1.46	21	9.5	6.55
				221	2.85				
				217	2.70				
	Vertical	58/44	82	260	{2.84 {2.76	10.86	28	9.5	5.78
				283	2.48				
				276	2.28				

* By acetylene method (Grollman, A.: Am. J. Physiol. **88**: 432, 1929).
† By cyanide method (Robb, G. P., and Weiss, S.: Am. Heart J. **8**: 650, 1933).
‡ By method of Moritz and von Tabora (Moritz, F., and von Tabora, D.: Deutsches Arch. f. klin. Med. **98**: 475, 1910).
§ By vital red method (Keith, N. M.; Rowntree, L. G., and Geraghty, J. T.: A Method for the Determination of Plasma and Blood Volume, Arch. Int. Med. **16**: 547, 1915).

known [16] that prolonged standing tends to reduce the plasma volume by the escape of fluid into the tissues. In case 3 the change in the blood volume was not significant.

14. McIntire, J. M., and Turner, A. H.: Venous Pressure and Posture in Normal Young Women, J. Clin. Investigation **14**:16, 1935.

15. Barach, J. H., and Marks, W. L.: Effect of Change of Posture—Without Active Muscular Exertion—on the Arterial and Venous Pressures, Arch. Int. Med. **11**:485 (May) 1913.

16. Thompson, W. O.; Thompson, P. K., and Dailey, M. E.: The Effect of Posture upon the Composition and Volume of the Blood in Man, J. Clin. Investigation **5**:573, 1928. Waterfield, R. L.: The Effects of Posture on the Circulating Blood Volume, J. Physiol. **72**:111, 1931.

Electrocardiogram.—Electrocardiograms taken with the subject in a horizontal and in a vertical position were obtained in cases 1 to 3. They all showed normal results, and, except for minor shifts in the axis and in case 2 a slight decrease in amplitude when the subject was erect, they showed no differences in the two positions. This is in agreement with most of the findings reported in the literature. In the case reported by Sanders,[21] however, there were slight differences in the origin of the T waves and in the elevation of the P waves in the two positions.

TABLE 6.—*The Effects of Drugs on Patients with Postural Hypotension in Horizontal and Vertical Positions*

Case	Dose, Mg.	Blood Pressure, Mm. of Mercury				Heart Rate			
		Before		After		Before		After	
		Horizontal	Vertical	Horizontal	Vertical	Horizontal	Vertical	Horizontal	Vertical
Atropine sulfate									
2	1.5 i.v.	174/88	102/69	165/90	100/74	74	78	82	88
	4.0 i.v.	128/72	94/56	144/78	75/54	72	80	80	80
3	1.5 i.m. and i.v.	114/79	55/46	142/98	60/48	65	75	82	90
4	0.5 i.v.	120/66	62/42	140/80	86/60	74	85	80	86
5	0.5 i.v.	120/82	75/60	132/92	106/80	102	108	113	116
Pilocarpine hydrochloride									
2	7.5 s.c.	126/70	62/48	136/78	70/48	72	80	76	76
3	7.5 s.c.	122/82	64/48	145/98	108/78	68	84	80	85
	15.0 s.c.	114/77	74/46	130/85	104/70	66	80	84	85
Epinephrine hydrochloride									
1	1.3 s.c.	105/71	*	122/70	70/60	85	..	96	110
2	1.3 s.c.	170/84	78/60	180/85	95/65	71	76	80	80
3	1.0 s.c.	118/80	58/46	148/70	62/38	60	84	96	96
4	1.0 s.c.	132/62	90/56	147/70	95/48	72	85	86	86
5	1.0 s.c.	123/79	94/60	126/77	100/65	110	114	112	114
Ergotamine tartrate									
2	1.0 s.c.	110/60	68/50	182/90	174/86	77	80	70	70
3	0.5 s.c.	136/90	80/60	150/92	105/76	56	78	56	66

* Control on another day: blood pressure, 120/84 (horizontal) to 65/55 (vertical); pulse rate 86 (horizontal) to 100 (vertical).

Pharmacologic Observations.—Atropine (Table 6): In three of the four patients studied atropine administered intravenously in moderate doses failed to increase the heart rate significantly, although its general effects on the pupils and salivation were manifest. In the fourth patient a fairly large dose (1.5 mg. intravenously) increased the heart rate less than was expected. In case 2 the drug was administered to the limits of the patient's tolerance (4 mg. intravenously within twenty minutes) with little effect on the heart rate. The blood pressure with the patient recumbent was increased in all cases, but in only one of the four was

the fall in pressure when the patient stood lessened, and in no instance were the symptoms alleviated. This is in agreement with previous observations.[17]

Pilocarpine (Table 6): In cases 2 and 3 pilocarpine hydrochloride in doses of ⅛ and ¼ grain (8 and 16 mg.), respectively, administered subcutaneously produced sweating, showing that the anhidrosis of these patients was not due to a deficiency of the sweat glands themselves or of their innervation. This confirms previous observations.[18]

TABLE 7.—*The Effect of Ephedrine Sulfate on Patients with Postural Hypotension in Horizontal and Vertical Positions*

Case	Dose, Mg.*	Time	Blood Pressure, Mm. of Mercury		Heart Rate		Symptoms
			Horizontal	Vertical	Horizontal	Vertical	
1	45	Before	.....	.....	..	..	Dizziness
		After	.....	.....	..	..	Dizziness
2	22	Before	140/76	70/60	78	80	Temporary dizziness
		After	164/92	96/65	78	78	No dizziness
	45	Before	142/80	90/68	76	80	Dizziness
		After	138/80	94/64	76	82	No dizziness
	45	Before	176/94	80/64	84	85	Slight dizziness; "all gone" feeling
		After	144/80	78/62	84	90	Faintness but no dizziness
3	22	Before	112/75	52/36	72	84	Dizziness
		After	152/92	115/82	74	92	No dizziness
	22	Before	117/77	33/26	62	80	Dizziness; cannot stand
		After	122/81	36/30	78	116	No dizziness; difficulty in seeing and hearing
	22	Before	136/88	65/50	75	90	No dizziness
		After	152/90	99/70	70	96	No dizziness
	45	Before	124/76	84/58	98	103	Buzzing in ears; eyes blurred
		After	166/96	123/85	70	104	No symptoms
4	22	Before	126/66	64/50	76	84	Dizziness
		After	126/68	106/70	70	80	No dizziness
5	22	Before	120/76	78/56	101	110	Transient dizziness
		After	122/78	91/70	104	108	No dizziness

* Administered orally.

Epinephrine (Table 6): The fall in blood pressure was in no case prevented by epinephrine, and the symptoms persisted, except in case 2, in which dizziness was relieved. The only atypical effect of this drug noted was that the heart rate of these patients tended to increase less than one would expect from the dose given.

Ephedrine (Table 7): This drug abolished the dizziness of four of the five patients to whom it was administered. It is of interest that the relief of symptoms occurred irrespective of whether or not ephedrine lessened the fall in blood pressure when the patient stood.

17. Bradbury and Eggleston.[1] Ghrist and Brown.[22] Sanders.[23] Weis.[20]
18. Bradbury and Eggleston.[1] Barker.[21]

Ergotamine (Table 6): In cases 2 and 3 ergotamine greatly lessened the drop in blood pressure. One patient (case 2), however, stated that the dizziness or "all gone" feeling was still present when she stood, but the interpretation of the effectiveness of the drug was hindered by the marked substernal distress which occurred and which was of sufficient severity to make inadvisable a repetition of the procedure.

Postural Reflex in Neurologic Disease.—Four of the patients showed extensive lesions of the central nervous system. In one there was

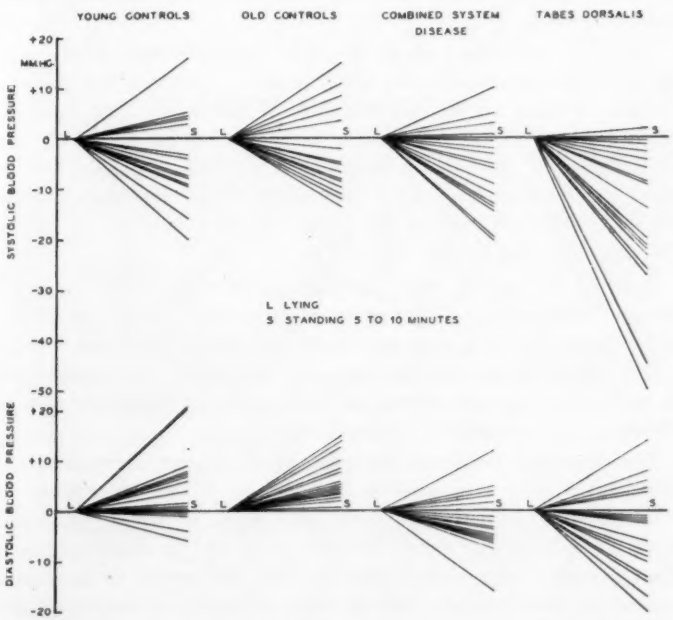

Chart showing the effect of standing on the systolic and diastolic blood pressures of control subjects and of patients with combined system disease or with tabes dorsalis.

definite, although not marked, evidence of disease of the central nervous system, while only one did not show any evidence of organic neurologic disease. In addition to these cases the postural changes in blood pressure in a group of patients with neurologic disease were studied. Repeated measurements were made with the patient recumbent and with the patient standing quietly for ten minutes. The blood pressure readings given in the accompanying chart represent the averages obtained in the period from five to ten minutes after the subject had stood up.

Two groups of control subjects were chosen: a group of healthy young adults ranging in age from 18 to 35 years and a group of older persons from 41 to 89 years old, all of whom were ambulatory hospital patients suffering from minor disorders, with no evidence of neurologic disease and no disturbance of the cardiovascular system other than the amount of arteriosclerosis consistent with their respective ages. The patients with tabes dorsalis all had Argyll Robertson pupils, those with combined system disease were ambulatory and no patient in either group had hypertension. Cases 4 and 5 are included among the charted cases of tabes dorsalis.

Our blood pressure findings in the two control series are in agreement with the results of other investigations on normal persons when allowance is made for the fact that most of the studies in the past have been made with the patient's arm at his side when he was erect. Our determination of the blood pressure with the patient standing and the arm supported at the level of the heart makes the average blood pressure, both systolic and diastolic, in this position about 3 or 4 mm. of mercury lower than it would be with the arm at the side.

None of the subjects with combined system disease showed definite postural hypotension. Although as a group they tended to show a somewhat greater drop than normal in the systolic blood pressure and a slight fall in the diastolic pressure, the deviations from normal were not sufficiently great to permit the conclusion that there was any disturbance of the sympathetic postural reflex.

The abnormal responses observed in the group of subjects with tabes dorsalis were more striking. In addition to the two patients with definite postural hypotension, there were three in whom the systolic pressure fell 20 mm. or more when they stood and the diastolic dropped 5 mm. or more. In five other patients either the systolic or the diastolic pressure fell abnormally. Thus in ten of seventeen patients with tabes dorsalis there was an abnormal postural response in the blood pressure.

In addition to these groups a miscellaneous group of subjects with disease of the central nervous system was studied. In none of them was the response of the blood pressure abnormal. These patients suffered from the following diseases: two had moderately advanced multiple sclerosis without evident cerebral involvement, one had marked syringomyelia including involvement of the cervical portion of the sympathetic chain on the left, one had amyotrophic lateral sclerosis, three had had transverse myelitis but the condition had improved so that they were able to walk and one patient with a Brown-Séquard syndrome from a cervical lesion had improved so that he was ambulatory.

COMMENT

The Normal Control of Blood Pressure.—The arterial blood pressure is controlled by the interrelation of three important factors: the output of the heart, the volume of the circulating blood and the peripheral vascular resistance. Perhaps the most important of these factors is the peripheral vascular resistance, the chief site of which is in the arterioles and to a lesser extent in the capillaries and possibly the venules. The degree of tone of the blood vessels which determines the resistance is partly an inherent property of the muscle itself, partly dependent on the nervous influences coming to it through the vasomotor nerves and partly influenced by circulating hormones.

The nervous control of the blood pressure is affected indirectly through the nervous influence on the heart rate and directly through the vasomotor nerves to the blood vessels by vasoconstriction and to some extent by active vasodilatation. It is possible that sympathetic centers exist in the spinal cord which have to do with the vasomotor tone, since it is known that the vascular tone below the level of an injury is regained in a patient who has suffered traumatic transection of the spinal cord, as well as in an animal with an experimentally severed spinal cord. The chief centers for the vasomotor control, however, lie in the brain. It has been shown [19] that vasoconstrictor centers exist in the floor of the fourth ventricle. Sympathetic and possibly parasympathetic centers also are present in the hypothalamus,[20] which are in part concerned with the vasomotor tone. Finally, a certain amount of control over the vasomotor reactions is exercised by the cerebral cortex, from centers probably confined to the premotor area.[21]

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19. Ranson, S. W., and Billingsley, P. R.: Vasomotor Reactions from Stimulation of Floor of Fourth Ventricle, Am. J. Physiol. **41**:85, 1916.

20. Karplus, J. P., and Kreidl, A.: Gehirn und Sympathicus: II. Ein Sympathicuszentrum im Zwischenhirn, Arch. f. d. ges. Physiol. **135**:401, 1910; Gehirn und Sympathicus: IV. Mitteilung, ibid. **171**:192, 1918; Gehirn und Sympathicus: VII. Ueber Beziehungen der Hypothalamuszentren zu Blutdruck und innerer Sekretion, ibid. **215**:667, 1927. Beattie, J.; Brow, G. R., and Long, C. N. H.: Physiological and Anatomical Evidence for the Existence of Nerve Tracts Connecting the Hypothalamus with Spinal Sympathetic Centres, Proc. Roy. Soc., London, s.B **106**:253, 1930. Ranson, S. W.; Kabat, H., and Magoun, H. W.: Autonomic Responses to Electrical Stimulation of Hypothalamus, Preoptic Region and Septum, Arch. Neurol. & Psychiat. **33**:467 (March) 1935.

21. Eulenberg, A., and Landois, L.: Ueber die thermischen Wirkungen experimenteller Eingriffe am Nervensystem und ihre Beziehung zu den Gefässnerven, Virchows Arch. f. path. Anat. **68**:245, 1876. Danielopolu, D.; Radovici, A., and Aslan, A.: Einfluss der Hirnrinde auf die Vasomotoren, Ztschr. f. d. ges. Neurol. u. Psychiat. **132**:671, 1931. Pinkston, J. O.; Bard, P., and Rioch, D. McK.: The Responses to Changes in Environmental Temperature After Removal of Portions of the Forebrain, Am. J. Physiol. **109**:515, 1934. Kennard, M. A.: Vasomotor Disturbances Resulting from Cortical Lesions, Arch. Neurol. & Psychiat. **33**:537 (March) 1935.

The Normal Postural Adaptation of the Blood Pressure.—When a human being undergoes marked postural changes, as in rising from a recumbent to an erect position, alterations must occur in the cardiovascular system in order to compensate for the altered hydrostatic conditions.[22] The compensation is usually prompt and adequate, so that only minor changes occur in the blood pressure and heart rate. The systolic blood pressure remains essentially unchanged; it may rise or fall slightly but rarely more than 10 mm. of mercury. The diastolic blood pressure usually increases slightly, and the pulse pressure in consequence is somewhat decreased. The heart rate increases from 10 to 20 beats per minute. Although perhaps it has not been proved, the evidence points to the fact that this is accomplished by means of sympathetic stimulation of the heart and blood vessels. The site of the vasomotor center involved is not definitely known.

Physiologic Variations in Postural Adaptation.—Under certain physiologic conditions the postural adaptation of the blood pressure may be inadequate and may even result in symptoms such as dizziness or fainting due to cerebral anemia. When this adaptation is insufficient, the inadequacy may occur immediately on assumption of the upright position, with subsequent full compensation, or, more commonly, the initial compensation is excellent but as standing is maintained the adaptation gradually becomes inadequate.[23] In the latter case, as the erect position is maintained the systolic pressure falls steadily, although not markedly, the diastolic pressure usually is maintained or may even progressively increase and the heart rate increases continuously. Dizziness or fainting may occur sooner or later and often comes on with great abruptness. In some instances the postural vasomotor reflex may be delayed, as when there is a temporary initial fall in the blood pressure, or it may occur with insufficient intensity. In most cases, however, the chief cause is impairment of the intrinsic vascular tone or poor tone in the skeletal musculature, especially of the abdomen and legs. The postural reflex operates not only normally but often excessively, as

22. (*a*) Schellong and Heinemeier.[11b] (*b*) Ellis, L. B., and Haynes, F. W.: Personal observations. (*c*) Ellis, M. M.: Pulse Rate and Blood Pressure Responses of Men to Passive Postural Changes, Am. J. M. Sc. **161**:568, 1921. (*d*) Schneider, E. C., and Truesdall, D.: A Statistical Study of the Pulse Rate and the Arterial Blood Pressures in Recumbency, Standing, and After a Standard Exercise, Am. J. Physiol. **61**:429, 1922. (*e*) Turner, A. H.: The Adjustment of Heart Rate and Arterial Pressure in Healthy Young Women During Prolonged Standing, ibid. **81**:197, 1927. (*f*) Ghrist, D. G.: Variations in Pulse and Blood Pressure with Interrupted Change of Posture, Ann. Int. Med. **4**:945, 1931. (*g*) Turner, A. H.; Newton, M. I., and Haynes, F. W.: The Circulatory Reaction to Gravity in Healthy Young Women: Evidence Regarding Its Precision and Its Instability, Am. J. Physiol. **94**:507, 1930.

23. Schellong and Heinemeier.[11b] Ghrist.[22f] Turner, Newton and Haynes.[22g]

shown by the marked tachycardia and maintenance of or even increase in the diastolic pressure. Nevertheless, blood continues to pool in the dependent venous areas, gathering there either because of a deficient venous tone or because of failure of the skeletal muscles to assist properly in the venous return. The heart receives and pumps progressively less blood, until finally cerebral anemia results.

This deficient postural adaptation is seen frequently in persons convalescent from a severe infection and in persons debilitated from any cause whatever. Patients with marked vasomotor instability are likely to exhibit it. Lewis [24] has commented on its occurrence in cases of effort syndrome. Mild degrees of insufficient adaptation are especially likely to result in symptoms when, in addition, other factors tending to promote cerebral anemia exist, e.g., cerebral arteriosclerosis or an initial low blood pressure.

Postural Hypotension.—Postural hypotension differs from the common type of inadequate postural adaptation. It is characterized by an immediate, marked and persistent fall in both the systolic and the diastolic pressure and frequently by a failure of the usual increase in the heart rate. The physiologic studies of the hemodynamics of the circulation made in cases 2 and 3 indicate that the total blood flow through the body is well maintained.

The only positive finding, therefore, in the physiologic study of the circulation of these patients was the great decrease in the arterial blood pressure. Why, then, does the pressure fall, and why do cerebral symptoms ensue? These subjects evidently fail to have reflex vasoconstriction when in a standing position, which would compensate for the increased hydrostatic pressure. This hydrostatic increment, therefore, tends to cause blood vessels lying below the level of the heart to dilate and to accommodate more blood. As a result there is a shift in the distribution of blood in the vascular bed, and although the heart pumps out an adequate amount, the blood circulates mainly through the dependent areas. The regions above the level of the heart, notably the brain, receive an inadequate circulation, and symptoms ensue. The extent of blood flow through the regions below the level of the heart depends on the result of two opposing factors. On the one hand, the dilatation of the arterioles tends to increase the blood flow, whereas, on the other hand, the dilatation of the capillaries and veins tends to cause temporary stagnation of the blood and a slowed blood flow. Although the possibility cannot be definitely excluded that a paradoxical vasomotor reaction may take place when the patient stands, i. e., an active dilatation, it appears unnecessary to predicate such a hypothesis. It is of interest

24. Lewis, T.: The Soldier's Heart and the Effort Syndrome, New York, Paul B. Hoeber, Inc., 1919, p. 19.

that the level of the blood pressure at which symptoms first occurred and fainting took place varied greatly in our patients and in those reported in the literature, not only between subjects but in the same person at different times. This variation must be due to alterations in the state of the cerebral blood vessels, that is, to varying degrees of arteriosclerosis, and in the same subject to changes in the cerebral vascular tonus.

The deficiency in the compensatory vasoconstriction involves the vascular areas both of the splanchnic region and of the legs, because the drop in blood pressure is partially abolished by eliminating the circulation through the legs by occluding pressure cuffs.

ETIOLOGY

The cause for this disturbance in compensatory postural vasoconstriction lies undoubtedly in a failure of the normal vasomotor reflex to operate. That it is an abnormality in the sympathetic nervous system is suggested also by the frequent occurrence of anhidrosis in these patients. It has been shown that the disturbance is generalized, and therefore either the site of the lesion must be in a sympathetic center or an afferent pathway controlling the entire reflex response or it must be a widespread disturbance of the efferent pathways or nerve endings.

As will be discussed later, it is probable that the etiology of postural hypotension is multiple and that under certain conditions the reflex arc may be interrupted at different levels. An interesting observation in this connection was that of Brown, Craig and Adson,[25] who noted that postural hypotension develops in patients with hypertension when all the sympathetic fibers have been removed from vessels below the diaphragm by resection of the anterior roots from the sixth thoracic to the second lumbar vertebra. Evidence can be presented, however, that in many of the clinical cases the disturbances lie within the central nervous system, probably within the brain. Moreover, postural hypotension of greater or less severity is not an infrequent accompaniment of disease of the central nervous system. It is possible that when the anatomic pathways of this reflex have been traced with greater exactitude, the measurement of blood pressure in different bodily positions may furnish evidence as to the presence or location of a lesion of the central nervous system.

A diminution or absence of the normal acceleration of the heart rate caused by standing is frequently but not invariably seen in association with postural hypotension, and its occurrence tends to aggravate the fall

25. Brown, G. E.; Craig, W. Mc.K., and Adson, A. W.: The Treatment of Severe Essential Hypertension: Effects of Surgical Procedures Applied to the Sympathetic Nervous System, Minnesota Med. **18**:134, 1935.

in blood pressure. It, too, is undoubtedly due to a sympathetic disturbance which could theoretically be located in the reflex arc involved.

With the exception of case 5, the abnormal responses which have been elicited in patients with orthostatic hypotension can all be explained on the basis of a disturbance of the sympathetic system, without assuming that the parasympathetic system is involved, as suggested by Ghrist and Brown. Failure of the heart to accelerate when the subject stands or after atropinization can be adequately explained by an absence of sympathetic stimulation. In case 5 the persistent tachycardia may have been due to paralysis of the vagus nerve.

1. *The Postural Reflex in Disease of the Central Nervous System.*—In their original description of postural hypotension Bradbury and Eggleston commented on the occurrence of indefinite changes in the central nervous system. Such vague changes were observed also by Ghrist and Brown in one of their cases.

Strisower [2e] was the first to point out the association of postural hypotension with tabes dorsalis. He said that he considered the disorder to be due to a disturbance of the vasomotor regulation, probably due to involvement of the centers in the spinal cord which regulate the blood pressure. In addition, he said that he believed that there must also be a depression of the vagus reflex to explain the failure of the heart to accelerate.

Allen and Magee [2m] mentioned that the hemianopia and aphasia which occurred in the case cited by them could not be explained by the postural hypotension alone, and they assumed the presence of patchy sclerosis of the cerebral vessels as a cause of these phenomena. The two patients reported on by Gainshorn and Horton [2n] exhibited extensive involvement of the central nervous system, including evidence of disturbance of the sympathetic innervation of the brain. The patient cited by Croll, Duthrie and MacWilliam [2p] showed a pseudo-Argyll Robertson pupil on one side and absence of the knee jerks, although examination of the spinal fluid revealed no abnormality.

Four of our patients showed marked and one showed definite though slight evidence of disease of the central nervous system. We have shown also that a disturbance of the postural blood pressure reflex is frequently observed in patients with tabes dorsalis, since it occurred in ten of the seventeen patients studied. On the other hand, it is evident from a consideration of the patients with combined system disease and with miscellaneous neurologic lesions that extensive disease of the central nervous system, especially of the spinal cord, can exist without a disturbance of the postural blood pressure reflex.

When a disturbance of this reflex does occur, where is the site of the lesion? The presence of Argyll Robertson pupils in all the cases of tabes was evidence of a disease affecting the brain. The third

patient, who was suffering from syringomyelia, showed definite evidence of involvement of the brain as well as of the cervical region of the spinal cord.

Further and conclusive evidence that the postural blood pressure reflex passes through centers in the brain and is not a spinal reflex is presented by case 6, the patient in whom traumatic section in the upper portion of the dorsal region of the spinal cord had occurred. In this patient there was reproduced as nearly as possible in a human being the condition of the "spinal animal," with complete severance of the control of the brain from the spinal cord. The fact that marked postural hypotension occurred in this patient indicates that the reflex arc was interrupted, this undoubtedly having taken place in the pathways leading from the brain.

The exact locus within the brain of the site of the center controlling this reflex cannot be stated with certainty, but it appears most reasonable that it is located in the hypothalamic area. This view is supported not only by the generally held concept that this region is concerned with somewhat more integrative functions than the hindbrain, but also by the fact that in the patients with tabes suffering from a disturbed postural reflex there exists a syphilitic lesion producing the pupillary changes in a region close to the sympathetic center in the hypothalamus [26] which might involve either the center directly or, more probably, the sympathetic fibers coming from it.

The second patient exhibited certain signs consistent with an early stage of combined system disease of the spinal cord but no objective evidence of involvement of the sympathetic centers in the brain. Although it is conceivable that involvement of the efferent sympathetic pathways in the spinal cord occurred which abolished the normal postural reflex, there is no corroborative evidence for this theory. It would be particularly hazardous to stress this theory in view of the fact that the fifteen patients suffering from combined system disease of greater severity than that in case 2 in no instance exhibited a definitely disturbed postural reflex.

2. *The Rôle of the Carotid Sinus.*—It has been suggested by Laubry and Doumer,[21] Hering,[27] Heymans,[28] Ask-Upmark [29] and others that

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26. Merritt, H. H., and Moore, M.: The Argyll Robertson Pupil: An Anatomic-Physiologic Explanation of the Phenomenon, with a Survey of Its Occurrence in Neurosyphilis, Arch. Neurol. & Psychiat. **30**:357 (Aug.) 1933.

27. Hering, H. E.: Ueber die Blutdruckregulierung bei Aenderung der Körperstellung vermittels der Blutdruckzügler und das Zustandekommen der Ohnmacht beim plötzlichen Uebergang vom Liegen zum Stehen, München. med. Wchnschr. **74**:1611, 1927.

28. Heymans, C.; Bouckaert, J. J., and Regniers, P.: Le sinus carotidien et la zone homologue cardio-aortique, Paris, Gaston Doin & Cie, 1933, p. 286.

29. Ask-Upmark, E.: The Carotid Sinus and the Cerebral Circulation, Lund, Berlingska Boktryckeriet, 1935, p. 266.

failure of the postural adaptation may be due to a disturbance of the regulating function of the carotid sinus and aortic depressor nerve. It has been shown [27] that in experimental animals in which denervation of these areas has been carried out postural hypotension occurs. In spite of the suggestiveness of this finding, it is not justifiable to apply the conclusions unequivocally to human beings. Since man, in contrast to the lower animals, is constantly subjecting himself to marked changes in bodily position, he may have acquired a more intricate or widespread postural reflex. The possibility that other vascular regions than the carotid sinus or the aortic arch may be concerned in initiating this reflex in human beings cannot be excluded.[30] Although there is no direct evidence that hypo-excitability of the carotid sinus is at times responsible for postural hypotension in human beings, the possibility cannot be excluded. In our cases the evidence that was available was against the hypothesis that a lesion of the carotid sinus is etiologically responsible.

3. *Disturbances of the Endocrine Glands.*—Several instances of postural hypotension associated with disease of the endocrine glands have been reported. Duggan and Barr [2h] studied a patient with Addison's disease who showed a marked drop in blood pressure when he stood, with associated vomiting and extreme dizziness. Ghrist [22f] has shown that a certain proportion of the patients with Addison's disease react to postural change with a marked fall in the blood pressure and an exaggerated rise in the pulse rate. In case 1 of the present series, although a diagnosis of Addison's disease could not be definitely made, there was considerable clinical and pathologic evidence favoring the diagnosis of a destructive lesion of the adrenal cortex. In view of the absence of other demonstrable etiologic factors, it is possible that such a lesion may have been responsible for the postural hypotension in this case. The reaction may in part be due to general hypofunction of the sympathetic nervous system and in part to the generalized muscular hypotonicity and weakness which are noted in this condition and which in themselves would hinder the adequate return of venous blood with the subject in the erect position.

A relationship between postural hypotension and hypofunction of the pituitary gland has been claimed by Schellong.[2d] He has found that this syndrome occurs in patients with clinical features suggesting Simmonds' disease and that it may be relieved by injections of a preparation of the anterior lobe of the pituitary gland. The evidence presented by Schellong of unequivocal diseases of the pituitary gland in his cases and of specific relief following the administration of an extract of the anterior lobe of the pituitary gland is insufficient to warrant a definite

30. MacWilliam, J. A.: Postural Effects on Heart-Rate and Blood-Pressure, Quart. J. Exper. Physiol. **23**:1, 1933.

ascription of an etiologic rôle to the pituitary gland. However, it is possible that certain disturbances of the glands of internal secretion may so affect the functioning of the vasomotor system that postural hypotension occurs.

4. *Toxic Agents or Trauma.*—Whether toxic agents or trauma ever produce postural hypotension is uncertain. One of the cases of this syndrome which have been reported [4] apparently followed a blow in the abdomen, and in another [2g] the symptoms were initiated by the sensation of something breaking loose in the abdomen. This raises the question of whether the structure of the splanchnic nerve may not have been damaged. Tripodi [3] has ascribed the cause in one of his cases to over-indulgence in tobacco smoking, but the evidence in this instance that tobacco was the etiologic agent is unconvincing.

In the light of the accumulated evidence, therefore, it may be considered that postural hypotension is a syndrome of multiple etiology. Frequently it is caused by demonstrable disease of the central nervous system, which either involves the sympathetic centers or acts on the sympathetic pathways. Disease of the endocrine glands, especially the adrenal cortex, may in certain instances be associated with this condition. In some cases, often when the symptoms are transitory, the syndrome may occur in vasomotor neurosis or during severe nervous exhaustion.[21] Whether trauma or external toxic agents cause it is as yet uncertain. Finally, there remains a group of patients showing postural hypotension in whom no specific etiologic cause can be found. For the present, the term idiopathic must be employed for the condition in this group. Whether in any of these cases the condition is due to hypo-excitability of the carotid sinus cannot be stated, but there is no direct evidence in favor of this possibility.

TREATMENT

The treatment of postural hypotension resolves itself into three aspects: treatment of the underlying condition, mechanical measures and drug therapy.

If an etiologic cause can be demonstrated, it should be vigorously treated if possible. Mechanical measures, such as tight bandaging of the legs or abdomen or both, sometimes offer considerable relief. Physical therapy may justifiably be given to a patient with general debility or nervous exhaustion, but otherwise it has been found to be of little or no valúe.

The most valuable pharmacologic agent which has been employed is ephedrine. Its use was originally suggested by Ghrist and Brown. In about half the cases in which it was tried the drug has given symptomatic relief. The usual dose employed is from 25 to 50 mg. by mouth as frequently as necessary. It has been assumed that the beneficial effect of ephedrine lies in its action in lessening the fall in the blood

pressure when the patient is in the erect position and in maintaining it above a critical level. While a certain amount of the improvement may be due to this peripheral effect, it is probable that the central action of ephedrine on the brain cells or cerebral circulation also plays an important rôle, and in some instances at least it is entirely responsible for the resulting benefit. This is demonstrated in our cases, as well as in the case reported by Barker and Coleman, in which dizziness was abolished after the administration of 25 mg. of ephedrine sulfate, regardless of whether the blood pressure fell to the same level when the patient stood as it did before the drug was given. It is known that ephedrine exerts a central action, the nature of which is not understood, and that it is used with benefit in certain cases of narcolepsy.

Ergotamine tartrate, when administered parenterally, lessens the postural hypotension and may relieve the dizziness to some extent. The use of this drug for this purpose was first suggested by Barker.[21] This effect is probably gained through the direct constricting action of the drug on the walls of the vessels. The likelihood of unpleasant side-effects, its relatively transitory action and the necessity of administering the drug by injection limits its usefulness.

A preparation of the anterior lobe of the pituitary gland, has been employed with apparent benefit by Schellong [2d] and Rudsit,[4] but the results were not sufficiently convincing to be accepted without further confirmation.

SUMMARY AND CONCLUSIONS

Six cases of postural hypotension are reported. In four there was definite evidence of neurologic disease (tabes dorsalis, syringomyelia and hematomyelia), and in an additional case there was some evidence of involvement of the central nervous system.

The vascular responses were tested, and in two patients measurements of the circulatory dynamics were made. The total blood flow was found to be well maintained when the patient was in the erect position.

The effects of atropine, pilocarpine, epinephrine, ergotamine and ephedrine were studied. Ephedrine was the most effective in relieving the symptoms.

The effect of postural change on the blood pressure of patients with tabes dorsalis, combined system disease and miscellaneous neurologic lesions was studied. Ten of seventeen successive patients with tabes had an abnormal postural response of the blood pressure.

The etiology and mechanism of postural hypotension are discussed. Postural hypotension results from a failure of the normal sympathetic vasomotor reflex to produce vasoconstriction when the subject assumes an erect position. It has been shown that the center controlling this reflex lies in the brain and not in the spinal cord. Since the disturbance

is widespread, the site of the lesion is either in a sympathetic center or in an afferent pathway controlling the entire response, or it is generalized throughout the efferent pathways or nerve endings. It is probable that multiple etiologic causes exist, but many instances of postural hypotension are associated with disease of the central nervous system.

NOTE.—Since the submission of this article for publication several additional papers on postural hypotension have been published or have come to our attention. Hughes and Yusaf [31] have reported a case, which, however, is more suggestive of poor adaptation than of true failure of the postural reflex. Alvarez and Roth [32] and Bickel and Demole [33] have each reported an additional case, and the latter authors have stressed, as have we, the importance of disease of the central sympathetic centers and pathways in the etiology of the condition. Bickel and Demole have also cited certain references on the subject, the originals of which are not available to us. Another reference which we have been unable to consult is that of Colombatti and Springer.[34]

Dr. Tracy J. Putnam, of the Neurologic Service, and Dr. Donald Munro, of the Neurosurgical Service, gave permission for the publication of the reports of cases 1, 3, 4 and 6. Drs. R. B. Capps and E. B. Ferris Jr. made certain of the observations on the vascular responses.

31. Hughes, T. A., and Yusaf, M.: Lancet **1**:1101, 1935.
32. Alvarez, W. C., and Roth, G.: Proc. Staff Meet., Mayo Clin. **10**:483, 1935.
33. Bickel, G., and Demole, M.: Rev. méd. de la Suisse Rom. **56**:1, 1936.
34. Colombatti, M., and Springer, G.: Gior. med. d. Alto Adige **7**:364, 1935.

TREATMENT OF TYPHOID WITH AN ANTITOXIC ANTITYPHOID SERUM

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DETROIT

The preparation of any standardized antitoxic serum of a reliable concentration depends on the possibility of measuring the antitoxic content of the serum in terms of its power to prevent specifically a biologic reaction to a definite amount of toxin. The lack of such a specific biologic phenomenon for the detection and measurement of the toxins derived, for instance from Bacillus typhosus, Meningococcus, Bacillus coli and Pfeiffer's bacillus, has served to delay the preparation of therapeutic serums of uniform potency. With serums such as the antimeningococcic serum, which are presumed to owe their therapeutic value to the presence of bactericidal properties, the possibility exists that the presence of undetermined amounts of antitoxin may explain the generally recognized variability in therapeutic efficacy.[1]

The discovery by one of us (G. S.[2]) of the phenomenon of local cutaneous reactivity to bacterial filtrates has offered a new biologic reaction by means of which a soluble antigenic toxin can be recognized in bacteria hitherto assumed to produce only endotoxins of poor antigenicity. Conversely, it has been shown that the antitoxic content of a therapeutic serum can be precisely measured by its ability to neutralize or prevent specifically the biologic effect of the toxin.

In its application to the culture filtrates of B. typhosus this phenomenon has made it possible also to demonstrate the existence of B. typhosus toxic substances identical or closely related to true exotoxins.[3] These soluble bacterial substances were obtained under con-

From the Laboratories and the Medical Service of the Mount Sinai Hospital, New York; and the Charity Hospital, and the United States Marine Hospital, New Orleans.

1. Shwartzman, G.: Therapeutic Antimeningococcus Serum, J. A. M. A. **93**: 1965 (Dec. 21) 1929.

2. Shwartzman, G.: J. Exper. Med. **48**:247, 1928.

3. Shwartzman, G.: J. Exper. Med. **49**:593, 1929; **50**:513, 1929; **54**:1, 1931; Klin. Wchnschr. **9**:41, 1925 and 1974, 1930.

ditions which allow little cell autolysis (in young "agar washings" cultures). By the injection of the filtrates into large animals immune antitoxic serums were developed which neutralize the toxic substances specifically and in multiple proportions.[3]

PREVIOUS OBSERVATIONS

Attempts to develop a specific serum therapy for typhoid have been made by numerous investigators. The difficulties encountered in the past were mainly due to the lack of a specific biologic reaction for measuring the potency of the therapeutic serums employed (horse, goat and sheep). Estimation of their therapeutic potency was usually based on the agglutination titer of the serum. In some instances (Berner Institute serum [Tavel] used by Spirig[4] and Du Mesnil[5]) bacteriolysis and antiendotoxic tests (Chantemesse,[6] Kraus and Stenitzer[7] and Besredka[8]) were employed as well as protection tests against live B. typhosus cultures in guinea-pigs (Klemperer and Levy,[9] Rodet,[10] Grasset and Gory[11] and Lüdke[12]). Favorable therapeutic results were reported with some of the serums (Chantemesse and Widal,[13] Kraus and Stenitzer,[14] Rodet,[15] Berner Institute serum,[16] Burroughs and Wellcome serum,[17] Grasset and Gory serum[11] and the Besredka serum used by Andriescu and Ciuca[18]), especially if they were administered in the early stages of the disease, usually during the first two weeks. The reports of subsequent investigators seem to have discredited some of these claims (Bertoye and Etienne Martin[19] with Rodet's serum).

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4. Spirig, W.: Cor.-Bl. f. schweiz. Aerzte **28**:385, 1898.
5. Du Mesnil: München. med. Wchnschr. **49**:1238, 1902.
6. Chantemesse, A.: Gaz. d. hôp. **71**:397, 1898.
7. Kraus, R., and von Stenitzer, R.: Wien. klin. Wchnschr. **20**:344, 1907.
8. Besredka, A.: Ann. Inst. Pasteur **20**:149, 1906.
9. Klemperer, F., and Levy, E.: Berl. klin. Wchnschr. **32**:601, 1895.
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11. Grasset, E., and Gory, M.: Compt. rend. Soc. de biol. **98**:435, 1928. Grasset, E.: J. M. A. South Africa **4**:380, 1930.
12. Lüdke, H.: München. med. Wchnschr. **59**:907, 1912.
13. Chantemesse, A.: Bull. et mém. Soc. méd. d. hôp. de Paris **36**:11, 1913. Brunon: Bull. Acad. de méd., Paris **45**:275, 1906. Josias, A.: Méd. mod. **13**:181, 1902.
14. Kraus, R., and von Stenitzer, R.: Deutsche med. Wchnschr. **37**:577, 1911. Forsmann: ibid. **37**:1936, 1911.
15. Rodet.[10] Etienne, G., and Gerbaut: Rev. méd. de l'est **61**:445, 1933. Louyot: ibid. **61**:449, 1933. Remond, A., and Minvielle: Bull. Acad. de méd., Paris **73**:321, 1915.
16. Spirig.[4] Du Mesnil.[5]
17. Pope, F. M.: Brit. M. J. **1**:259, 1897. Cooper, P. R.: ibid. **1**:518, 1897. Baskett, B.: ibid. **1**:423, 1903. Cowen, T. R. J.: Lancet **2**:778, 1899.
18. Andriescu, C., and Ciuca, M.: Ann. Inst. Pasteur **27**:170, 1913.
19. Bertoye, P., and Martin, P. E.: Lyon méd. **143**:723, 1929.

The therapeutic value of these antityphoid immune serums has been discredited on other grounds also. The antibodies which were demonstrable in the serums (bacteriolysins, agglutination and complement-fixing antibodies) apparently have no bearing on the processes of recovery from an acute infectious disease. The so-called antiendotoxic serums fail to neutralize these endotoxins specifically and in multiple proportions. The effect of endotoxins on test animals were shown by Pfeiffer and Bessau,[20] Zinsser [21] and more recently by Murray [22] to be irregular in their effect.

The interesting results obtained with the serum of Grasset and Gory [11] depended on the protection of guinea-pigs against subcutaneous infections with live B. typhosus. Unfortunately, no accurate determination of the potency of the serum is possible under the experimental conditions described by these authors.

TECHNIC

The following methods were employed in the preparation of the antityphoid antitoxic serum employed by us in the treatment of typhoid and in the determination of its potency before therapeutic trial.

Horses were immunized for several months by weekly subcutaneous and intravenous injections. Some of the serums recently employed were obtained from horses which had received two or three weekly injections. For the subcutaneous injections bacteria-free filtrates, "agar washings" culture filtrates and in some instances tryptic-digest broth culture filtrates of B. typhosus were used. The initial dose varied from 1 to 5 cc., and the amount was gradually increased to 20 cc. For the intravenous injections heat-killed vaccines of several strains of B. typhosus were used. The initial dose was from 3 to 5 cc. of vaccine containing approximately 1,000,000,000 micro-organisms per cubic centimeter. On subsequent injections the dose was gradually increased to 10 cc. Higher concentrations of the vaccine were then made, containing 5,000,000,000 micro-organisms per cubic centimeter, and the dose was gradually increased until 10 cc. was finally used. It is possible to continue the immunization of horses with B. typhosus culture filtrates and vaccines in this manner for a considerable length of time. It should be remembered, however, that the materials are toxic. Sometimes, a small amount of filtrate kills a horse. Rises in temperature, cutaneous abscesses and systemic shock are frequently observed. In case of shock a horse can often be saved by epinephrine given immediately or within a few hours after the injection of the immunizing material and later by large bleedings. The abscesses are easily relieved by incision and the evacuation of pus.

The ability of a horse to produce antibodies is subject to considerable individual variation. Moreover, antibodies capable of neutralization of the phenomenon under discussion may unexpectedly drop in titer. For this reason, it seems impor-

20. Pfeiffer, R., and Bessau, G.: Zentralbl. f. Bakt. (Abt. 1) **56**:344, 1910.

21. Zinsser, H.; Parker, J. T., and Kuttner, A.: Proc. Soc. Exper. Biol. & Med. **18**:49, 1921.

22. Murray, E. G. D.: The Meningococcus, Medical Research Council, Special Report Series, no. 124, London, His Majesty's Stationery Office, 1929.

tant that the large bleeding be made as quickly as possible after the trial bleeding. This is carried out as follows: The necessary groups of rabbits are prepared by intradermal injections of the B. typhosus "agar washings" filtrates on the morning of the day before the trial bleeding. On the morning of the trial bleeding the rabbits then receive an intravenous injection of the mixtures to be titrated. The results are read early in the afternoon of the same day. If an adequate antitoxin titer is found, a large bleeding is performed on the same afternoon, i. e., about six or eight hours after the trial bleeding.

A sudden rise or drop in concentration of the phenomenon-neutralizing antibodies is a conspicuous feature and may be observed in various periods of uninterrupted immunization. Once a drop occurs, continuation of immunization is frequently valueless. A rest of several weeks or months may reestablish the ability of a horse to produce neutralizing antibodies. After the rest period one or more injections are frequently sufficient to bring about a high concentration of antitoxin, which in turn may promptly drop again after an additional injection. Rises and drops in concentration of the antibodies can be elicited several times in the same horse by alternating periods of immunization with periods of rest. The toxic filtrates alone without the aid of vaccines are capable of stimulating the production of neutralizing antibodies as well as of agglutinins and precipitins.

During several years of experimental immunization of horses, phenomenon-neutralizing antibodies of numerous batches of serum were tested against toxic substances derived from various strains of B. typhosus and also derived from rough and smooth variants. The results reported previously[23] can be summarized as follows: Various stock strains of B. typhosus were found to produce reacting factors (toxins) which differed in their neutralizability by antistock immune horse serums. Of four stock strains chosen for this work, two occupied extreme positions. One showed a high degree of neutralizability with serums that were strain homologous and strain heterologous. Another strain showed only irregular neutralizations with the same serums. The remaining two stock strains occupied intermediate positions in the degree of consistent neutralization. Toxic substances derived from rough variants of B. typhosus were not neutralized by antistock serum but acquired a new antigenic specificity. It was found also that cutlivation of B. typhosus strains on human blood produced important changes in the neutralizability of B. typhosus toxic substances.

In developing the antityphoid serum it seemed important, therefore, to employ toxic substances derived from strains of various neutralizability as well as toxic substances derived from strains of B. typhosus cultured on human blood. Toxic substances derived from rough variants also were employed, because the formation of rough variants may be expected in vivo in the course of an infectious disease of prolonged duration, such as typhoid. For these reasons polyvalent filtrates and vaccines consisting of toxic substances derived from various strains and variants were used for the immunization of the horses. Incidentally, it should be mentioned that the employment of strains grown on human blood broth brought about the formation of antihuman serum precipitins.

Titration of B. Typhosus Toxins.—The rabbits used for titrations were each given an intradermal injection of 0.25 cc. of undiluted B. typhosus "agar washings" filtrate. The animals were divided into groups of three. Twenty-four hours later a single intravenous injection of the filtrate, diluted in an 0.85 per cent solution of sodium chloride, was given to each rabbit. The dose was 1 cc. per kilogram of body weight. Each group of rabbits received intravenously a

23. Shwartzman, G.: J. Exper. Med. **52**:781, 1930.

different dilution of the filtrate. The local reactions were read four or five hours after the intravenous injections were given. The titrations were carried until the lowest dilution was found which gave no reaction in the three rabbits tested, as well as the highest dilution which gave reactions in one or more rabbits of the group. The minimal dose of the toxin was then considered as lying between these two figures. If a given filtrate was employed for any length of time, repeated control titrations were made. In these control tests the dilutions employed were both the highest dilution capable of eliciting a reaction and the lowest dilution giving no reaction. This was necessary since a loss of potency occurred during storage of the filtrates, as well as an occasional increase of the potency.

Titration of Serum Neutralization of B. Typhosus Toxins.—Into an area on the skin of the abdominal wall of a rabbit was injected 0.25 cc. of the undiluted filtrate. From twenty-two to twenty-four hours later a single intravenous injection was given of a mixture of the same filtrate (diluted previously in an 0.85 per cent solution of sodium chloride to the desired degree) with undiluted horse serum in the proportion of four to one. The mixtures prepared on the morning of the experiments were incubated in a water bath at 37.5 C. for one hour. The precipitate in the mixture was broken up by shaking immediately before the injection. The intravenous dose of the mixture was 1.25 cc. per kilogram of body weight. The readings of the reactions were made four or five hours after the intravenous injection. Each mixture was tested in three rabbits. If no reactions were obtained in the three rabbits tested, the result was considered as showing complete neutralization of the toxin. If one or two of the three rabbits tested showed reactions, the result was recorded as showing irregular neutralization.

Thus, the maximum amount of reacting factors completely neutralized by 0.25 cc. of a given serum was used to compute the neutralizing titer. As was noted in the experiments described, a constant amount of serum was titrated against increasing amounts of the filtrate. The danger of error arising from possible variations in susceptibility to small amounts of toxins was thus avoided. The neutralization tests proved consistent on repeated reexaminations of the same batches. This has been confirmed by innumerable tests of samples of the serum during the last three years.

The agglutination and precipitation tests were carried out in the usual manner.

CLINICAL OBSERVATIONS

Seventy-eight patients with typhoid received from 100 to 500 cc. of unconcentrated serum intravenously. If preliminary intradermal or ophthalmic tests revealed definite sensitivity, no serum was given. Each patient received an injection of 10 cc., followed three hours later by 25 cc. If there were no untoward symptoms, 50 cc. was given slowly by the intravenous drip method. Either of these procedures was repeated at intervals of from four to eight hours with similar amounts until the total dose was introduced. The usual complications of intravenous serum therapy were encountered and are reported in detail later in the paper. The results of observations with the antityphoid serum are summarized in the accompanying table.

Effect on Toxemia.—Thirty-nine, or 50 per cent, of the patients showed relief from toxemia following the injection of the serum. In

Name	Diagnosis*	Duration of Temperature, Days	Serum Given, Day of Disease	Effect of Serum on Temperature†	Serum Sickness‡	Toxemia§	Comment
L. K.	3, 2	47	11	0	++	+	Relapse two weeks later
L. R.	3, 2	30	11	0	+	0	
F. A.	3, 2	93	21	0	0	+	
P. L.	3, 2	38	7	0	+	+	
M. F.	3, 2	30	13	0	++	+	
E. T.	3, 2	44	18	0	A++	+	Otitis media and ethmoiditis
A. N.	3, 2	33	9	+	++	+	
L. R.	3, 2	48	12	+	A	+	
C. A.	3, 2	47	21	0	++	+	
J. M.	3, 2	38	9	0	++ (2)	+	
G. G.	3, 2	36	8	+	++	+	Cholecystitis
M. G.	3, 2	34	13	+	A+	+	
J. K.	3, 2	39	10	?	++	+	
C. A.	3	43	18	?	++	+	Low grade fever apparently associated with pyelitis
L. E.	2, 3	21	11	?	++	+	Clinically typhoid; no laboratory data
M. B.	3, 2	40	10	0	+	+	
C. W.	3, 2	50	15	0	+	+	
E. S.	3, 2	40	17	0	+	0	
H. L.	3, 2	50	13	0	+	++	First treated with normal horse; later with immune serum
O. C.	3, 2	30	22	+	+	+	
G. W.	3, 2	23	9	+	++	+	
C. R.	3, 2	26	14	+	++	+	
C. B.	3, 2	20	10	+	+	+	
M. S.	3, 2	18	10	+	++	++	Died of perforation during convalescence
H. J.	3, 2	27	20	+	+	+	
B. R.	3	21?	7	+	++	+	
B. S.	3, 2	21	16	+	0	+	Case described in text
R. W.	3, 2	34	12	+	+	+	
B. K.	3, 2	43	10	+	++	+	
R. S.	3, 2	27	13	+	++	?	
S. P.	3, 2	19	11	+	0	+	
T. G.	3, 2	45	7	+	+	+	
M. D.	3, 4	22	11	+	+	+	Typhoid relapse on the 36th day followed by measles
C. C.	3	20	9	+	+	+	
J. M.	3	23	9	+	+	+	Clinically unquestionable typhoid; no laboratory data
J. P.	2, 3	21	8	+	+	+	
W. H.	3, 4	19	15	+	0	+	Profuse intestinal bleeding; stopped a few hours after administration of serum
J. W.	3	25	18	+	+	+	Clinically unquestionable typhoid; no laboratory data; disappeared a few hours after administration of serum
O. M.	3	26	10	+	+ (2)	?	Clinically unquestionable typhoid; no clinical data
L. C.	3, 2	46	9	0	++	0	Serum of low potency
J. B.	3, 2	36	14	+	+ (2)	+	
N. C.	3, 2	43	12	0	+	?	
B. F.	3	43	18	+	0	?	Complicated by measles
M. W.	3, 2	109	11	+	0	+	
J. Y.	2, 3	48	13	0	+ (4 times)	0	Mild case from onset
E. E.	3, 2	53	9	0	++	?	Relapse on 42d day
G. A.	3, 2	43	12	0	+ (several)	?	
M. C.	3, 2	45	12	?	+	?	
D. K.	3, 2	14	11	?	?	?	Pneumonia and acute rheumatic endocarditis; died
J. P.	3, 2	31	17	+	+	0	Serum discontinued and started again 12 days later when patient was moribund; died
C. S.	3, 2	30	16	?	+	0	
S. M.	3, 2	50	13	0	0	+	
L.	3	60	25	0	+	+	Low grade fever between 32d and 60th day
A. C.	3, 2	21	17	?	?	0	Died of pneumonia, lower lobes of both lungs

* 2 indicates positive blood culture; 3, clinically positive typhoid, and 4, stool positive for B. typhosus.

† 0 indicates no effect; ?, unfavorable effect, and +, favorable effect.

‡ 0 indicates no serum sickness; ?, moderate; +, severe, and ++, immediate anaphylaxis.

§ 0 indicates no effect; ?, questionable effect; +, favorable effect, and ++ very favorable effect.

Data on the Effect of Antityphoid Antitoxic Serum on Typhoid—Continued

Name	Diagnosis	Duration of Temperature, Days	Serum Given, Day of Disease	Effect of Serum on Temperature	Serum Sickness	Toxemia	Comment
E. B.	3, 2	35	10	0	+	0	Early preparation of serum of low potency
G. K.	3, 2	61	17	0	+	0	Early preparation of serum of low potency
S. O.	3, 2	45	37	—	++ (19th)	0	
H. R.	3, 2	59	15	0	+	0	Early preparation of serum of low potency
W. W.	3, 2	40	16	0	+ (22d)	0	Early preparation of serum of low potency
R. H.	3, 2	7	6	—	++	0	Died
F. M.	3, 2	35	12	0	A++	0	30 cc. of serum of low potency
L. S.	3, 2	37	14	0	+	0	
J. R.	3, 2	81	20	0	0	0	
H. W.	3, 2	28	9	0	0	0	Early preparation of serum of low potency
F. A.	3, 2	37	14	0	+	0	Small amount of serum; early preparation of serum of low potency
F. M.	3, 2	54	15	0	?	0	
V. G.	3, 2	34	13	0	+	0	
O. C.	3, 2	57	10	0	0	0	
W. B.	3	40	7	0	+	0	
V. C.	3, 2	41	13	0	+ (2)	0	
C. L.	3, 2	60	22	0	0	0	
A. P.	3, 2	43	13	0	+	0	
F. R.	3, 2	45	12	0	+	0	
A. P.	3, 2	9	8	—	0	0	Bronchopneumonia; died
G. D.	3, 2	42	10	0	+	0	
S. W.	3, 2	28	12	0	+	0	
G. G.	3, 2	?	9	0	+	0	Bronchopneumonia; died
S. H.	3, 2	45	8	0	0	0	Cholecystitis after 20th day
F. G.	3	22	14	0	++	0	In spite of some relief effect reported questionable because only 50 cc. of serum was given

some of the cases this effect was dramatic; a patient who had been in a low muttering, delirious state, with incontinence of stools, would be sitting up in bed and looking and acting as if he were not sick forty-eight hours after the administration of serum. In thirty-two cases the serum had no effect on the toxemia, and in seven the effect was so slight as to be questionable.

Effect on the Duration of the Disease.—An exact statement as to the duration of fever in any given case presents many difficulties. The history was often vague as to the date of onset; the clinical picture was frequently obscured by fever due to complications, intercurrent infection or serum sickness. Fifty-six of the patients who received serum treatment showed a rise in temperature for over thirty days. In twenty-two cases the duration was less than thirty days.

Effect on the Temperature.—Twenty-five patients showed a mean fall in temperature following the injection of serum. In some of these cases the fall followed so promptly the giving of serum and occurred so early in the disease that we feel that the serum may have played the important part. In some cases the fall in temperature occurred at the time when defervescence normally begins, and the part played by the serum is discounted.

The records of the temperature in three of the cases illustrate the sudden and dramatic change in the disease in these cases and the totally unexpected end of the disease within a few days.

Case 1.—This patient seemed to be dying. He was in an extremely toxic state, was constantly delirious and disoriented and made involuntary motions. Blood culture showed B. typhosus. The spleen was palpable, and there was pronounced leukopenia. From the eighth to the tenth day of the illness 102 cc. of

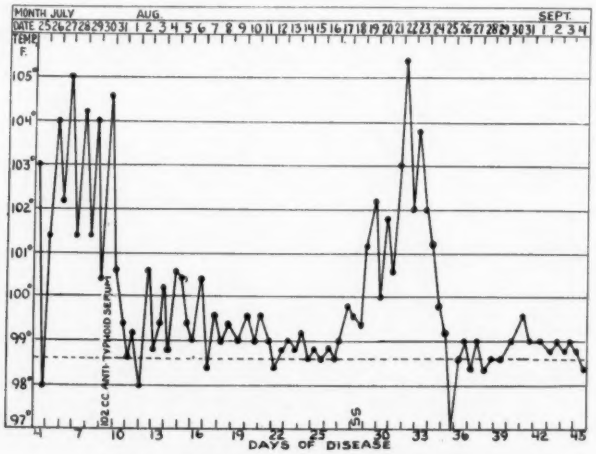

Chart 1.—Data on the temperature in case 1.

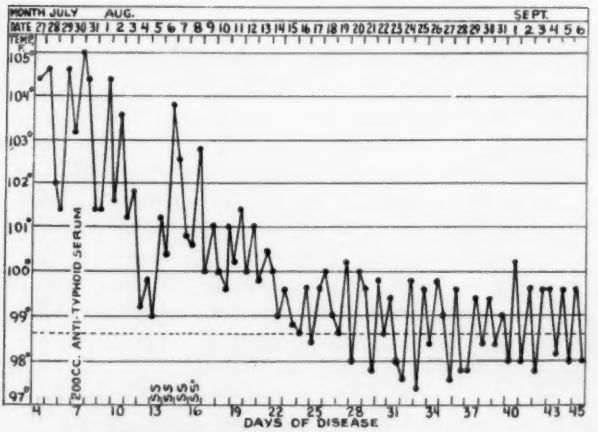

Chart 2.—Data on the temperature in case 2.

serum was given. A most dramatic effect was noted on the fever. The temperature fell to normal, and the disease apparently terminated on the eleventh day. Blood cultures were repeatedly sterile thereafter. Although all other clinical manifestations of typhoid disappeared, a postinfectious psychosis persisted, in spite of a normal temperature for three weeks after the end of the disease.

CASE 2.—This patient was admitted to the hospital on the third day of the disease. She was in a moderately toxic state. The temperature reached 104.6 or 105 F. daily. A total of 200 cc. of antityphoid serum was administered on the sixth and seventh days of the disease. On the eighth day the patient appeared less drowsy; on the ninth day the temperature began to drop and was normal on the eleventh day of the disease. Serum sickness developed six days after the injection of serum, and was marked by fever, urticaria and polyarthritis which persisted for three days. The agglutination titers (Widal tests), which showed negative results before the injection of serum, were 1:1,280 on the eighth, ninth and twelfth days of the disease, dropped to 1:320 on the thirty-third day of the disease and subsequently became negative again.

CASE 3.—This patient was admitted on the sixth day of illness. He was acutely ill and in a typhoidal and moderately toxic state. The temperature ranged between 100.4 and 106 F. during the three days before serum was administered. A total of 485 cc. of antityphoid serum was injected intravenously during fifteen

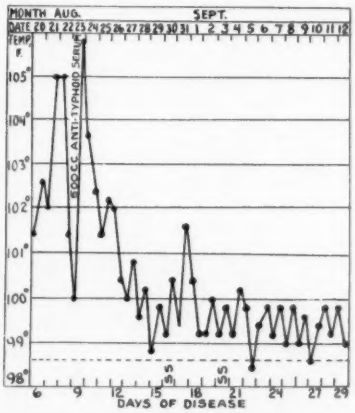

Chart 3.—Data on the temperature in case 3.

and one-half hours. Within twenty-four hours following the injection of the serum the temperature dropped to normal (i. e., on the twelfth day of the disease) and remained normal thereafter, with the exception of a peaklike rise to 101.8 F. on the afternoon of the eighth day after the last injection of serum. The rise was coincident with the development of serum sickness, which manifested itself in urticaria and pruritus.

Twenty-four hours after the injection of serum, i. e., on the tenth day of illness, the Widal test, which had previously shown negative results, reached a titer of 1:320.

Serum Sickness.—Facilities for the concentration of the antityphoid antitoxic serum were not readily available. It was necessary, therefore, to employ large quantities of unconcentrated serum. The intravenous injection of such large quantities of horse serum resulted in the subsequent development of clinical manifestations of serum sickness in a large proportion of the cases.

The first manifestations of serum sickness began, as a rule, on or about the sixth day after the first injection. The symptoms in order of frequency were fever, urticaria, tachycardia and arthralgia. The serum sickness persisted for from two to five days. It showed a tendency to recur on or about the twelfth or the fourteenth day and again from the eighteenth to the twenty-first day after the injection was given. The second and third recurrences were sometimes more severe than the primary attack.

The symptoms of serum sickness were seldom alarming, but they brought discomfort to the patient and often obscured the clinical picture during the stage of recovery. The fever which usually accompanied the serum sickness frequently made it difficult or impossible to interpret the influence of the therapeutic serum on the temperature curve of

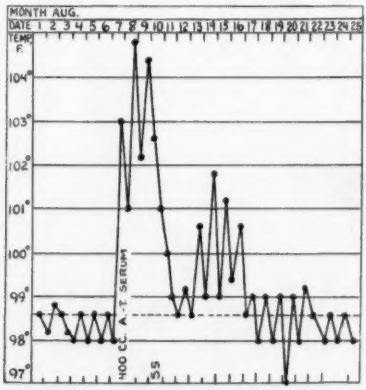

Chart 4.—Data on the temperature in a normal volunteer.

typhoid. This is illustrated by the accompanying temperature curve (chart 4) of a normal, afebrile volunteer who received an intravenous injection of 400 cc. of antityphoid horse serum.

As seen in this instance, there was an immediate rise in temperature to 104.8 F. following the injection of the serum. The temperature remained approximately at that level for the next twenty-four hours and then sharply dropped to normal within the second twenty-four hours. On the fifth day after the injection of serum typical manifestations of serum sickness developed, with the temperature fluctuating between 99 and 101.8 F., and the symptoms persisted for several days, until the temperature again became normal.

The occurrence of similar febrile periods of serum sickness following the injection of antitoxic antityphoid serum into patients with typhoid may have served to prolong the elevation of temperature and to obscure an otherwise obvious influence of the serum on the toxic manifestations of the illness and on the duration of the disease.

Fourteen patients showed no bad effect of any sort; thirty-nine had mild serum sickness, and twenty-two had severe serum sickness, i. e., a sharp rise in temperature, urticaria and arthralgia. Three patients had anaphylactic shock. Four patients had two attacks of serum sickness, and one patient had four.

Effect of Serum on Agglutinins for B. Typhosus.—In forty-seven cases Widal titrations were made shortly before the administration of serum, from one to three days after the injections were completed and frequently at short intervals until the patient was discharged. The analysis of the data obtained is as follows:

Twenty-two patients showed a marked rise in the agglutination titer which was unquestionably due to the injection of serum. In eighteen of these cases the Widal titer, which had been recorded previously as negative or in the range between 1:80 to 1:160, reached a titer of 1:1,280 within twenty-four hours after the administration of the serum. In three cases it reached a titer of 1:25,600; in another 1:10,000. In ten other cases there was a rise in titer up to a dilution of 1:640 following the administration of serum.

These results can be interpreted as being due to the injected serum, for the rise in the Widal titer occurred in the early stages of the disease immediately after the injection of the serum and in titers well above normal expectancy for the given stages of the disease. In four cases there was a doubtful effect of the serum on the agglutination titer, and in eleven cases no effect was observed.

Because of the small number of cases in each group it seemed to be difficult to draw any conclusions as to the correlation between the rise of the Widal titer following administration of serum and the therapeutic effect.

Effect on Bacteremia.—In twenty-two of the forty-two cases in which an unquestionable effect of the therapeutic serum on the toxic manifestations of the disease was noted the positive blood culture became sterile within forty-eight to seventy-two hours after the administration of the serum. Sterile blood cultures were also noted after the administration of serum in twelve cases of demonstrable bacteremia in which there was a moderate effect of the serum. In other words, the bacteremia cleared up within a few days after treatment with serum in thirty-four cases. In contrast to this result, the following case must be reported as unusual in our experience.

CASE 4.—This girl was given 400 cc. of serum between the fourteenth and the eighteenth day of illness because she was in a toxic and typhoidal state. The clinical picture changed within twenty-four hours, and at the end of forty-eight hours she was normally active, looked entirely well and had a good appetite. The temperature began to fall within twenty-four hours after the serum was administered and reached normal three days later. From that time on the temperature

remained normal, and the patient felt well. To our surprise, blood cultures taken on the fourth, eighth and tenth days of normal temperature showed B. typhosus, although clinically the patient was no longer suffering from typhoid or from any typhoidal complications. The first negative blood culture was obtained on the fourteenth day of normal temperature.

In this one instance B. typhosus bacteremia persisted for at least ten days after all the toxic manifestations of typhoid had apparently been completely neutralized by the antitoxin and the patient was clinically well.

Mortality.—In seventy-eight cases in which serum was administered there were seven deaths—a mortality of 8.9 per cent. One of the

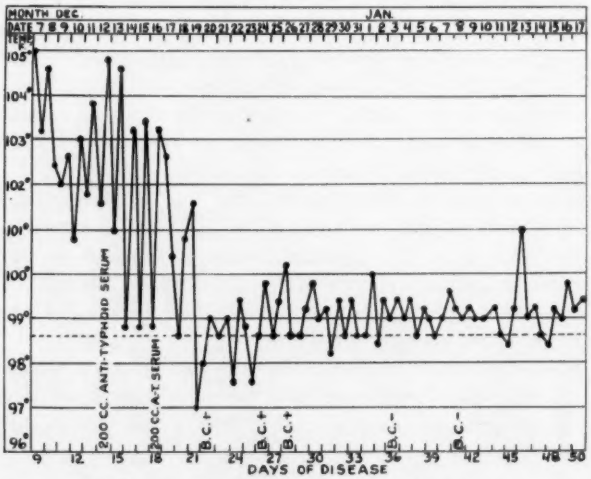

Chart 5.—Data on the temperature in case 4.

patients was moribund when serum was given; two died of pneumonia (one in thirty-six hours and one after an interval of two weeks) and one died of toxemia twelve hours after the serum was injected.

Controls.—A control series of patients with typhoid was studied in which equally large amounts of normal horse serum were used. Four of the seven persons so treated died—a mortality of 57 per cent. One patient was distinctly harmed by serum, two probably were harmed and one was distinctly benefited. That the results would be more valuable if an equal number of controls were used is unquestioned, but the high mortality among the controls following the administration of large quantities of normal horse serum definitely prohibited this procedure. The records of the Charity Hospital, New Orleans, for a period of three years, including the year of our work there, were collected and analyzed as a rough

control. There were two hundred and fifty-six cases of typhoid with fifty-six deaths—a mortality of just over 22 per cent. In 40 per cent of the cases the duration of fever was less than thirty days. The average duration of fever was thirty-eight days for this group. Among the patients who were given serum treatment the mortality was 8.9 per cent; 35 per cent had a duration of fever of less than thirty days, the average duration, including serum sickness, being thirty-eight days.

COMMENT

The average duration of fever and the percentage of cases in which the duration was less than thirty days when serum was administered are roughly identical with the results in the control series. The mortality of 9 per cent as against 22 per cent probably means little in a small number of cases.

Taking into consideration all the various effects, we are of the opinion that sixteen patients showed a definitely favorable effect, i. e., relief from toxemia, a fall in the mean temperature and a shortened duration of the disease, without any bad effects, such as serum sickness. These sixteen patients represented roughly 20 per cent of the total number who received serum treatment. In the series of patients treated with normal horse serum one patient in seven showed a distinctly favorable effect—14.3 per cent, which does not indicate a wide difference in a small series.

The high incidence of serum sickness with its added discomfort to the patient suffering from long-continued fever makes the use of unconcentrated serum unacceptable for general use. One of us (G. S.) is now working on the problem of making a more concentrated polyvalent serum.

As will be seen, our figures do not justify the assumption of any very remarkable result. Against this, we have often obtained the distinct clinical impression that marked relief from toxemia resulted in certain of the cases. This change must be observed to be appreciated, and it is the only thing on which we base our hopes for further treatment along this line.

In conclusion we wish to state that the work reported is of a purely experimental nature and that the serum in its present form is not advocated for general therapeutic use. The report is made in order to bring out the possible beneficial effects of an antityphoid antitoxic serum, the preparation of which is made possible by the development of the phenomenon of local cutaneous reactivity to bacterial filtrates.

ALTERNATION OF THE HEART SOUNDS

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Volhard [1] in 1905 studied the characteristic sphygmographic features in cases of pulsus alternans and reported that by listening to the heart one could recognize a conspicuous alternation of the second heart sound in all the cardiac cycles and of the first heart sound in only three or four cycles after each extrasystole. This alternation of the sounds revealed itself through modifications in their intensity and pitch; the sounds in the cycle with a large pulse beat were more intense and of a higher pitch than those in the cycle with a small pulse beat.

Although the initial fact was verified at the beginning of the present century, there are only a few cases reported in the medical literature in which alternation of the heart sounds was recognized on auscultation (Meyer and Levy [2] and Morris [3]). With the exception of Morris,[3] all other authors who have been interested in alternation of the heart sounds as a manifestation of alternation of the heart beats (Wenckebach and Winterberg,[4] Mackenzie,[5] Lian,[6] Laubry,[7] Clerc [8] and Edens [9]) expressed the opinion that alternation of the heart sounds is exceptional

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1. Volhard, F.: Ueber den Pulsus alternans und pseudoalternans, München. med. Wchnschr. **7**:590, 1905.

2. Meyer, A., and Levy, R.: Un cas de pouls alternant sans hypertension et avec alternance des bruits du cœur, Presse méd. **32**:131, 1924.

3. Morris, R. A.: The Clinical Recognition of Pulsus Alternans, J. A. M. A. **87**:463 (Aug. 14) 1926.

4. Wenckebach, K., and Winterberg, H.: Die Unregelmässige Herztätigkeit, Leipzig, Wilhelm Engelmann, 1927.

5. Mackenzie, J.: Les maladies du cœur, Paris, Félix Alcan, 1920.

6. Lian, C.: Aparato circulatorio, in Tratado de patologia medica, Barcelona, Editorial Pubul, 1924.

7. Laubry, C.: Maladies du cœur et des vaisseaux. Nouveau traité de pathologie interne, Paris, Gaston Doin, 1930.

8. Clerc, A., and Deschamps, N.: Cœur et vaisseaux, Paris, Masson & Cie, 1931.

9. Edens, E.: Die Krankheiten des Herzens und der Gefässe, Berlin, Julius Springer, 1929.

and is likely to be found only in rare cases of alternation of the pulse beats of unusually high degree.

Convinced that "method is all in the progress of science," we studied the quality of the sounds in patients with alternation of the heart sounds, using for this purpose phonocardiographic records—a method that we consider trustworthy.

Kahn [10] in 1911 had already taken advantage of the use of a record of the heart sounds as a means of studying certain facts in circulatory dynamics in alternation of the heart beats experimentally produced in animals by the injection of glyoxylic acid. The goal of this author differed from our own; also, the conditions of his experiments (exposed heart) were different.

MATERIAL AND METHOD

For our study we employed seven patients with pulsus alternans. In six (cases 1, 2, 3, 4, 5 and 6) the alternation was independent of respiration, and in the other patient (case 7) it was related to respiration, the respiratory rate being nearly

Summary of Data on Patients with Alternation of the Pulse Beats

Case Number	Heart Rate	Breathing Movement	Degree of Alternation of Pulse	Strong Contraction						Weak Contraction					
				First Heart Sound	Second Heart Sound	Duration of Systole, Seconds	Delay of the Pulse Wave, Seconds	QRS Complex	T Wave	First Heart Sound	Second Heart Sound	Duration of Systole, Seconds	Delay of the Pulse Wave, Seconds	QRS Complex	T Wave
1	111	32	High	Strong	.....	24	16	Small	Large	Weak	.....	22	18	Large	Small
2	115	30	High	Strong	Weak	24	16	.....	.....	Weak	Strong	24	18	.....	.....
3	93	29	High	Strong	Weak	28	16	.....	.....	Weak	Strong	27	18	.....	.....
4	112	23	Slight	Strong	Strong	24	16	.....	.....	Weak	Weak	24	16	.....	.....
5	187	29	High	Strong	Weak	?	16	.....	Large	Weak	Strong	?	16	.....	Small
6	107	25	Mild	Strong	.....	26	16	.....	.....	Weak	.....	25	16	.....	.....
7	40	19	Mild	Strong	.....	36	16	.....	.....	Weak	.....	36	16	.....	.....

one-half the heart rate. In the first six patients the alternation persisted and was even more conspicuous with voluntary retention of respiration; in the other patient, alternation disappeared with voluntary suspension of respiration.

The six patients with true alternation of the heart beats presented the following conditions: ventricular paroxysmal tachycardia (case 5), syphilitic aortic incompetence (case 3), cardiac enlargement with arterial hypotension and heart failure (case 4), coronary arteriosclerosis (case 1) and high arterial pressure with heart failure (cases 2 and 6).

The only patient (case 7) with alternation of the pulse beat which was related to respiration had a permanent nodal rhythm; the heart rate was usually about 40 per minute and the respiratory rate about 19 per minute.

10. Kahn, R. H.: Studien am Phonokardiogramme, Arch. f. d. ges. Physiol. **140**:471, 1911.

The degree and intensity of the alternation were not equal in the seven cases and may be divided into three groups, according to the classification of White [11] and Morris.[3]

The alternation was of high degree in four cases (1, 2, 3 and 5) and could be detected easily by feeling the radial pulse. The alternation was of mild degree in two cases (4 and 7), and feeling the pulse was inadequate for its recognition, although it was recorded in the sphygmogram. The alternation was slight in the remaining case (6). It was impossible to detect the regular change in the amplitude of the pulse beats in this case by merely feeling the pulse, and it could not be recorded in the sphygmogram. It could be recognized only by listening to the arterial sound through a stethoscope placed over the brachial artery at the elbow under an inflated rubber cuff, the pressure of which was slightly inferior to the systolic pressure in the artery (fig. 1).

In each of the seven cases a record was obtained of the heart sounds, Frank's segmentary capsule, with the modifications introduced by Wiggers and Dean,[12] being used. The record was obtained with the receiver placed in the precordial region where a previous examination had revealed heart sounds of the greatest intensity. The patients were told to breathe slowly and then to interrupt their breathing in the expiratory phase, an interruption that was always of slight duration owing to the circulatory condition. Electrocardiographic and sphygmographic records were obtained simultaneously with the record of the heart sounds. For the electrocardiograms, an Einthoven electrocardiograph of standard type was used, and for the sphygmograms, an oscillographic Boulitte tambour. In four cases (1, 2, 3 and 4), simultaneously with the phonocardiogram, a phlebogram was obtained by means of Frank's segmentary tambour; in one case (7) a pneumogram was also made.

In the cases in which the alternation could be detected only by listening to the arterial sounds through a stethoscope placed below the inflated cuff, a graphic record of these sounds was obtained simultaneously with the other records. This was done by putting the receiver at the elbow on the brachial artery.

Before all these tracings were secured, complete clinical, roentgenographic and electrocardiographic observations were made on each patient.

The auscultatory findings were carefully checked by various expert observers for the purpose of excluding personal errors.

RESULTS

Phonocardiogram.—The series of groups of oscillations produced by the first heart sound showed an alternation in their height and size in each of the records obtained in the seven cases (figs. 2, 3, 4 and 5). A cardiac cycle with a strong first sound was followed by a cycle with a weak first sound and so on through many cycles. The difference in the size of the oscillations produced by a strong first sound and those produced by a weak first sound in two consecutive cycles varied greatly in the seven cases. In certain cases the difference was reduced to a minimum, as in cases 2 and 6 in which the oscillations produced by a weak first sound were nearly nine-tenths the size of those produced by a strong first sound. In the other cases (1 and 4) the difference was conspicuous; the oscillations

11. White, P. D.: Alternation of the Pulse: A Common Clinical Condition, Am. J. M. Sc. **150**:82, 1915.

12. Wiggers, C. J., and Dean, H.: The Principles and Practice of Registering Heart Sounds by Direct Methods, Am. J. M. Sc. **153**:666, 1917.

produced by a weak first sound were two-thirds the size of those produced by a strong first sound. In the remaining cases, those produced by a weak first sound were three-fourths (cases 3 and 5) and four-fifths (case 7) the size of the corresponding oscillations produced by a strong first sound.

The duration and the number of double oscillations were the same for the strong first sound as for the weak first sound in five cases (3, 4, 5, 6 and 7). In the other two cases the group of oscillations for a weak first sound was wider; that is, the sounds were of longer duration and were formed by a double oscillation more than the group for the strong first sound in the same record.

The series of groups of oscillations produced by the second heart sound had an alternating height in four of the seven cases (2, 3, 4 and 5). The analysis of the phonocardiographic records made in these four cases showed that a cycle with a strong second sound was followed by a cycle with a weak second sound and so on for many cycles. The difference between the size of the large and that of the small oscillations produced by the second sounds in two consecutive cycles was evident. The small oscillations were three-fourths the size of the large oscillations in case 3, two-thirds the size in cases 4 and 5 and one-half the size in case 2.

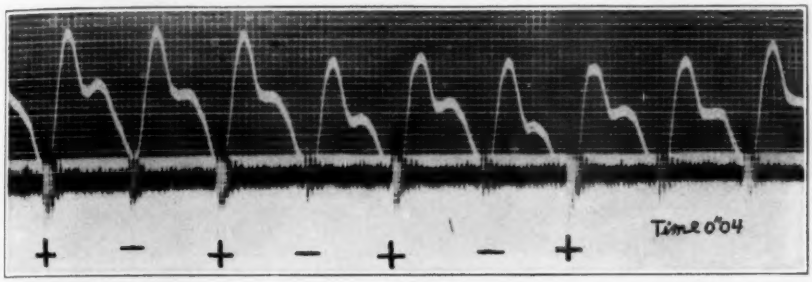

Fig. 1.—While the sphygmogram (upper section) does not show an alternation of the pulse waves, the record of the arterial sounds (lower section) shows the regular succession of a strong (+) and a weak (—) sound. The difference in the height of the pulse wave is due to breathing movement. Time, 0.04 second.

The duration, or width, of the group of large oscillations produced by the second sound was the same as that of the small oscillations of the following cycle in the four cases in which the alternation of the second sound could be detected on the graphic records. The number of double oscillations remained equally unaltered for both the strong and the weak second sounds in the four cases in which alternation in the amplitude or size of the oscillations was present.

In the four cases (2, 3, 4 and 5) in which there coexisted an alternation of the first sound with an alternation of the second sound, the alternation was discordant for the same cycle in three cases (2, 3 and 5) and concordant in the remaining case (4). In the graphic records obtained in three cases in which there was discordant or opposite alternation of the heart sounds, an analysis revealed the following facts: The cycle with a strong first sound had a weak second sound, and the cycle with a weak first sound had a strong second sound (figs. 3 and 5).

In the case in which a double alternation of the sounds was concordant in the same cycle, a strong first sound occurred with a strong second sound and a weak first sound with a weak second sound (fig. 2).

In four cases the interval between the beginning of the first sound and the beginning of the second sound was the same in the cycle with a strong first sound as in the cycle with a weak first sound. In the remaining three cases (1, 3 and 5) the interval was greater in the cycle with a strong first sound than in the one with a weak first sound.

Sphygmogram and Phonocardiogram.—The sphygmograms made in six cases, (1, 2, 3, 4, 5 and 7) showed the succession of a large pulse wave and a small pulse wave. In the other case (6) this succession of alternate large and small waves could be detected only by listening to the artery in the elbow and by obtaining a graphic record of the arterial sounds at this place (fig. 1).

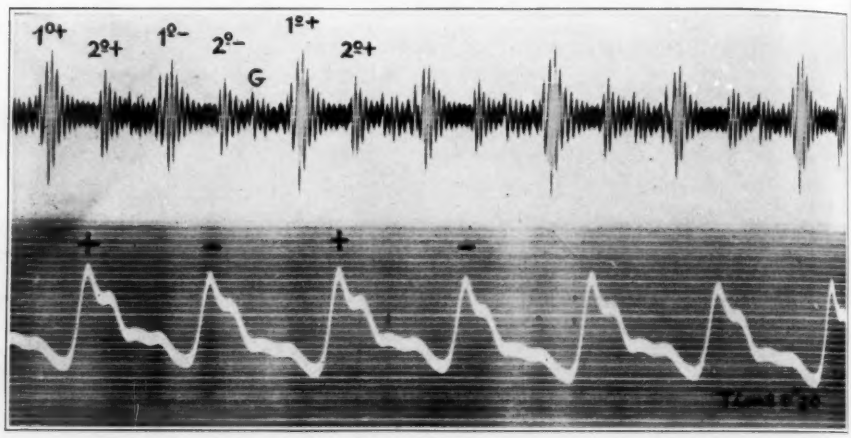

Fig. 2.—Alternation of the pulse beats (lower section) and of the heart sounds (upper section). The cardiac cycle that produces a large pulse wave (+) has both strong first sounds (1°+) and strong second sounds (2°+); that is, there is concordant alternation between the pulse beats and both heart sounds. *G* indicates protodiastolic gallop rhythm. Time, 20 seconds.

The interval between the large pulse wave and the small pulse wave that follows was equal to that between the small pulse wave and the following large pulse wave in four cases (4, 5, 6 and 7). In the three other cases (1, 2 and 3) the interval between the large and the small pulse wave was greater than that between the small and the following large pulse wave.

The sphygmogram made simultaneously with the record of the heard sounds in the seven cases showed that the strong pulse wave in the sphygmogram corresponded to the cycle with a strong first sound and, in the same way, that the small pulse wave corresponded to the cycle with a weak first sound. The correlation of the pulse waves with the alternation of second sounds that existed in four cases (2, 3, 4 and 5) was equal to that of the pulse waves with the first sounds in only one case. In the remaining cases the correlation was reversed; that is, a

large pulse wave corresponded with the cycle with a weak second sound and a small pulse wave corresponded with the cycle with a strong second sound (figs. 2 and 3).

The records of the pulse beats and the heart sounds made simultaneously revealed also the following facts: The delay in the appearance of large and small pulse waves, that is, the interval of time between the beginning of the first heart sound and the production of the pulse wave, was the same in four cases (4, 5, 6 and 7). The delay in the appearance of the small pulse wave was more conspicuous than that of the large wave in the three remaining cases (1, 2 and 3).

Electrocardiogram and Phonocardiogram.—The electrocardiogram showed an alternation of its complexes in only two of the seven cases (1 and 5). This alter-

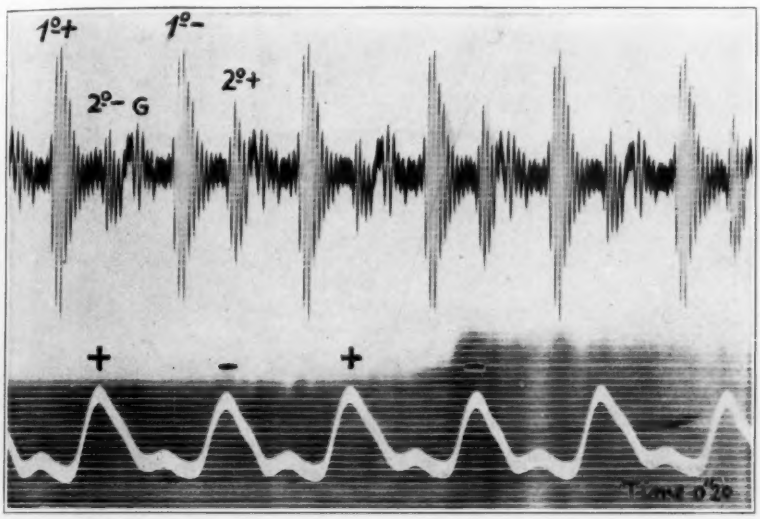

Fig. 3.—Alternation of the pulse beats (lower section) and of the heart sounds (upper section). The cardiac cycle that produces a large wave (+) shows a strong first sound (1°+) and a weak second sound (2°—); that is, there is concordant alternation between the pulse beat and the first sound and discordant alternation between the pulse beat and the second sound. *G* indicates protodiastolic gallop rhythm. Time, 20 seconds.

nation affected only the T wave in one case (5) and the QRS complex in the other case (1); in the latter there was also a slight alternation of the T wave.

The alternation of the T wave in case 5 could be seen in three or four successive complexes; after that it disappeared for a time, and then appeared again, and so on. The phonocardiogram obtained simultaneously showed alternation in the first and second sounds each time that there was alternation in the T wave in the electrocardiogram. A cycle with a large T wave corresponded to a cycle with a strong first sound and a weak second sound (fig. 5).

The alternation of the QRS complex in case 1 was present in the entire record. In this case, a cycle with a large QRS complex corresponded to a cycle with a weak first sound in the simultaneously registered phonocardiogram (fig. 4).

Pneumogram and Phonocardiogram.—In the only case in which the alternation of heart sounds was associated with the respiration, the pneumogram recorded simultaneously with the phonocardiogram showed that the first heart sound was stronger during inspiration and weaker during expiration (fig. 6).

Auscultation.—Listening to the heart revealed alternation of the heart sounds in the seven cases. In four (1, 3, 4 and 7) auscultation revealed alternation of only the first sound. In the other three cases both sounds were alternate. Alternation of the first sound was more easily recognized than alternation of the second sound in case 4, while alternation of the second sound was more conspicuous than alternation of the first sound in the other two cases (2 and 5).

The alternation of the sounds consisted in changes in their intensity and pitch and also in their cadence. After a cycle with an intense, high-pitched, dry sound

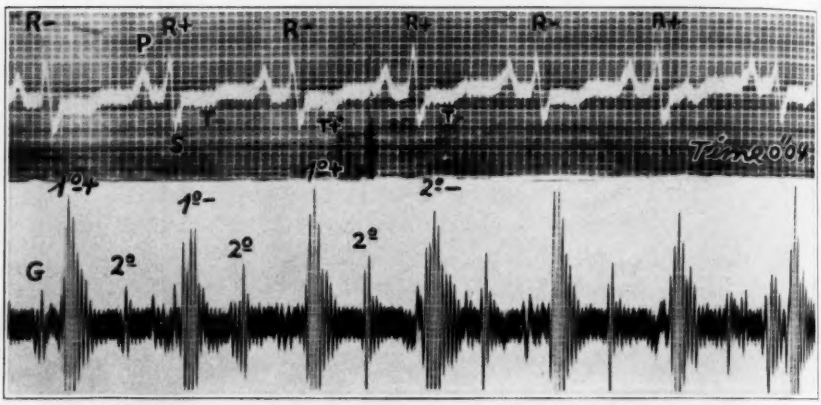

Fig. 4.—Alternation of the first sound (lower section) and of the QRS complexes (upper section). The cardiac cycle with a strong first sound (1°+) has a corresponding small QRS complex (—); that is, there is discordant alternation between the first sound and the QRS complex. *G* indicates presystolic gallop rhythm. Time, 0.04 second.

there followed one with a less intense, low-pitched, muffled sound, and so on, giving the sensation that the cycle the first sound of which was less intense was nearer to the sounds of the preceding cycle than to those of the following cycle, instead of being equidistant from both the following and the preceding sound.

To summarize, auscultation revealed alternation in the sounds only at certain moments; at other times it seemed as if the alternation had disappeared completely. During many cycles alternation of the sounds was easily recognized, but during many others it was less conspicuous and in some it seemed to be wholly absent.

Single premature beats were usually followed by conspicuous alternation in the sounds. This change was frequently confined to a few cycles. The alternation was easily recognized during voluntary retention of respiration save when it was associated with the respiratory movements.

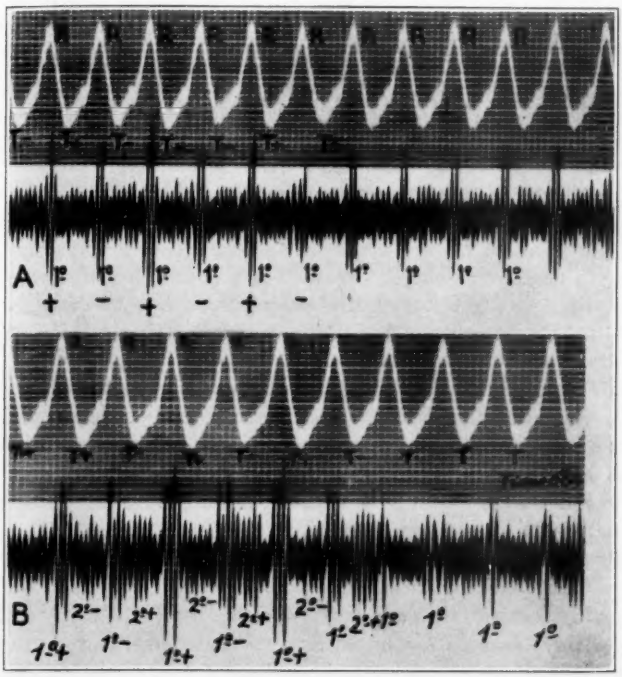

Fig. 5.—Alternation of the heart sounds (lower sections) and of the T waves (upper sections) in a case of paroxysmal ventricular tachycardia. The cardiac cycle with a large T wave (+) has a strong first sound (1°+) and a weak second sound (2°—); that is, there is concordant alternation between the first sound and the T wave and discordant alternation between the second sound and the T wave. *A* shows the part of the record where the alternation of the first sound is better appreciated. *B* is another part of the record where the alternation of the second sound is better appreciated. In both parts it may be seen how the alternation of the sounds stops when the alternation of the T wave ceases to produce itself. Time, 0.04 second.

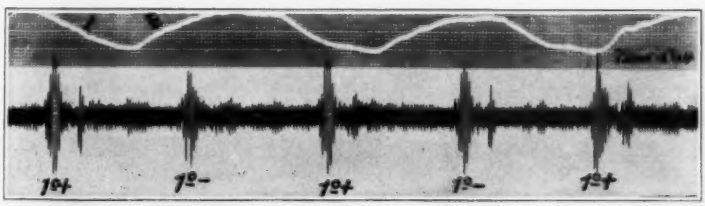

Fig. 6.—Alternation of the heart sounds (lower section) in relation to breathing movements (upper section). During the inspiration (*I*) the first sound (1°+) is strong. Time, 0.04 second.

COMMENT

Knowledge concerning circulatory dynamics in alternation of the heart has been gained by recording the heart sounds and by obtaining volume and pressure curves on animals in which alternation has been produced by different methods (Kahn;[10] Straub;[13] Wiggers[14]). The pressure curves have revealed the regular occurrence of a cycle with increased systolic intraventricular pressure followed by one with decreased systolic intraventricular pressure. The increased pressure produces what is known as a strong heart contraction, while the decreased pressure results in a weak contraction. The duration of the systole of a strong contraction is commonly a few hundredths of a second longer than that of a weak contraction. The same curves have also shown that the ventricular volume at the end of the systole of a strong contraction is smaller than that at the end of the systole of a weak contraction; that is, the systolic residue of the strong contraction is smaller than that of the weak contraction. The large or small quantity of blood thrown into the systemic arteries at every contraction is the cause of successive large and small pulse beats. A high pulse wave corresponds to the strong contraction. The pulse beats may succeed one another with perfect regularity, or a certain irregularity may be present though the rhythm of the heart remains perfectly regular. This irregularity is due to the greater delay of the small wave.

The abruptness of the increase in the intraventricular pressure at the beginning of the systole of the strong contraction is the cause of the increased intensity of the first sound as compared with the intensity of the same sound during a weak contraction in which the augmentation of intraventricular pressure is less abrupt. Just as a high pulse wave corresponds to a strong contraction, a strong first sound corresponds to a large pulse beat; that is, the alternation of the first sound is concordant with the alternation of the pulse beat. The fall of intraventricular pressure at the end of the systole, which is more abrupt in the strong contraction, is the cause of the increase in the intensity of the second sound as compared with the intensity of the same sound in the weak contraction, during which the fall of intraventricular pressure is less sudden. Just as a large pulse wave corresponds to a strong contraction, a strong second sound corresponds to a large pulse beat; that is, alternation of the second sound and alternation of the pulse beat are also concordant.

13. Straub, H.: Dynamik des Herzalternans, Deutsches Arch. f. klin. Med. **123**:403, 1917.

14. Wiggers, C. J.: The Dynamics of Ventricular Alternation, Ann. Clin. Med. **5**:1022, 1926.

The knowledge of these facts concerning the circulatory dynamics of alternation, discovered by experiments on animals, makes it unnecessary to comment further on the findings in our seven cases of pulsus alternans save as they relate to the alternation of the second sound, which, instead of being concordant, as has been encountered in experiments on animals, was found to be discordant in three of the four cases in which it was present.

Before we try to explain the possible causes of this disagreement between clinical and experimental findings, we must face the possibility of an error in the methods utilized by us. The resemblance of our findings to the clinical and experimental findings of others suffices to dismiss such a possibility. This view is strengthened by the following fact: In the only case of alternation of the heart sounds in man that we have found reported in the medical literature (Wiggers [15]), the second sound was discordant in its alternation with the pulse wave. Though the author did not state the fact, the graphic record published in his paper shows clearly that with an intense first heart sound there was a less intense second sound and vice versa. As the alternation of the first sound has until now been considered concordant with that of the pulse beat, alternation of the second sound must be considered discordant.

Considering the dynamic conditions in the strong and weak contractions, we believe that both sounds should be more intense in the strong than in the weak contraction.

Since we do not believe that the second heart sound can be less intense in the strong than in the weak contraction, we are of the opinion that the discordant alternation of the second sound, when compared with the alternation of the pulse beat (verified by ourselves in human beings), can be explained only by an alteration in the conditions that regulate the transmission of heart sounds from their original site to the place in the cardiac area where they are heard.

In a textbook recently written by one of us (C. P.[16]) it is stated that the acoustic phenomena taking place in the valves or in the cavities of the heart themselves reach the ear of the observer or the receiver of the registering apparatus in the following manner: The vibration spreads to the walls of the heart and from there to the thoracic walls.

The transmission of the sound from the heart to the thoracic walls takes place because of the intimate relation between the two, for the pulmonary tissue is a bad conductor of sound; that is, the heart sounds are heard easier when the transmission is good, and the transmission

15. Wiggers, C. J.: Modern Aspects on the Circulation in Health and Disease, Philadelphia, Lea & Febiger, 1923.

16. Cossio, P.: Semiologia cardiovascular, Buenos Aires, El Ateneo, 1935.

is directly associated with the degree of contact between the heart and the thoracic walls.

Volume curves have demonstrated that the volume of the heart at the end of the systole of a strong contraction is smaller than that at the end of the systole of a weak contraction. This means that at the end of the strong systole the relation between the heart and the thoracic wall is less intimate than at the end of the weak systole. The small degree of contact between the heart and the thoracic walls at the end of the strong systole causes a poor transmission of the acoustic phenomena which are produced in this moment, namely, the second heart sound. This explains why though the second sound of the strong contraction is originally stronger than that of the weak contraction, it is heard as if it were less intense.

To summarize, discordant alternation of the second sound, such as that observed in three of the four cases in which alternation was present, is produced because the second sound of the weak contraction is more apparent than the second sound of the strong contraction when listened to at the precordium. This is due to contact between the heart and the thoracic wall at the end of the systole of the weak and the strong contraction.

This explanation of discordant alternation of the second sound noted by us in three of four patients with alternation of the pulse beats makes it easy to understand the mechanism of concordant alternation in the other patient, whose record showed agreement between the height of the pulse beat and the intensity of the second sound. The conspicuous enlargement of the heart of this patient assured a perfect contact between the heart and the thoracic wall, notwithstanding the changes in the volume of the heart at the end of strong and weak contractions; that is, the transmission of the sounds from their original site to the region of precordium where they were audible was equally good in both contractions, therefore the increase of intensity of the second sound of the strong contraction over the second sound of the weak contraction.

The relation between alternation of the first sound and alternation of electrocardiographic complexes that was present in two cases followed strictly the relation between the complexes and the alternation of the pulse beats (Poumailloux;[17] Padilla and Cossio[18]). Alternation of the first sound was concordant with alternation of the T wave and discordant with alternation of the QRS complex just as the pulse wave was concordant with alternation of the T wave and discordant with alternation of the QRS complex.

17. Poumailloux, M.: Le pouls alternat, Paris, Masson & Cie, 1930.

18. Padilla, T., and Cossio, P.: Alternancia electrica ventricular, Semana méd. **1**:1573 (June 11) 1931.

The alternation of the first sound encountered in seven cases of alternation of pulse beats and the alternation of the second sound verified in four of the seven cases modifies the view held up to the present, namely, that alternation of the heart sound is exceptional. Moreover, it should be known that alternation of the heart sound is a frequent and perhaps constant manifestation of the alternation of the heart beat. The reason this fact has been so easily overlooked is that auscultation has been the only means of recognizing it. The failure to detect the alternation by auscultation is due to the mild degree in which it generally is present rather than to the fault of the method itself.

The acoustic phenomenon which expresses the alternation of the sounds is in no case so conspicuous as to become evident on auscultation. Generally it is within the limits of perceptibility, and if it is not deliberately sought it will be overlooked.

Failure to make a deliberate examination and ignorance of the manner in which the sounds are heard by the ear caused the alternation to be overlooked in case 1, notwithstanding careful auscultation of the heart. The alternation was revealed only when a graphic record was obtained to register the gallop rhythm that was present. After the alternation of the first sound was discovered in the graphic record it was detected by auscultation.

To eliminate the possibility of the sounds being heard by mere suggestion, the usual proofs and counterproofs were employed, and the presence of the alternation was confirmed.

A deliberate examination for alternation of the heart sounds and the knowledge that it could be heard with the ear made possible its recognition in the other six cases before any graphic record was obtained. Moreover, in two cases in which alternation of the pulse beats had escaped detection by feeling the pulse, it was discovered by listening to the heart sounds. The alternation was later confirmed by graphic records.

The alternation of the sounds is recognized by the ear by small changes in their intensity, pitch and sound from one cycle to the other; i. e., one sound is more intense, higher pitched and dryer than the same sound of the following cycle, and so on.

These sounds the intensity and pitch of which change alternately from one cycle to another may succeed one another regularly, or a certain irregularity may be present. In the later case it seems as if the sounds of the weak heart contraction should be nearer to the preceding, than to the following, cycle, instead of remaining equidistant from both. The slight irregularity which the ear can perceive is independent of cardiac rhythm, which remains regularly. The irregularity is due to

a real anticipation of the second sound in the cardiac cycle in which a weak first sound is produced by the shorter duration of the systole of this beat.

CONCLUSIONS

In seven cases in which different degrees of pulsus alternans were present the graphic record of the heart sounds showed alternation of the first sound in all cases and alternation of the second sound in only four cases.

The alternation of the first sound was concordant in all cases with the alternation of the pulse beats. In one case only it coexisted and was concordant with an alternation of the T wave in the electrocardiogram. In another case it coexisted and was discordant with an alternation of the QRS complex.

Alternation of the second sound was concordant with alternation of pulse beats in one case and discordant in three cases. The discordance between alternation of the second heart sound and the pulse beats is associated with its transmissibility from the site where it originates to the place where it is heard in the precordium.

Deliberate precordial auscultation and a mental image of the way the alternation of sounds is perceived enabled recognition of the alternation in all cases. In two of four cases in which alternation of the first and of the second sound was present, the alternation of the first sound was perceived easier than that of the second sound.

Alternation of the sounds is detected by means of auscultation by the slight differences in the intensity, pitch and sound that the same sound shows in two successive cardiac cycles. In certain cases there may be a slight typical change in cadence, namely, of the rhythm of their succession.

NEPHROSIS WITH UREMIA FOLLOWING TRANSFUSION WITH INCOMPATIBLE BLOOD

REPORT OF SEVEN CASES WITH THREE DEATHS

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AND
IRVING GRAEF, M.D.
NEW YORK

Since recognition and classification of the blood groups have become general, serious posttransfusion reactions have been infrequent. However, the publication of Bordley's [1] report has focused attention on a striking syndrome following transfusion with incompatible blood. He reported three such reactions and, after extensive search of the literature, fourteen adequately described additional instances. Subsequently other observers have published their experiences with this reaction.[2] The clinical and pathologic similarities in all the cases reported are striking. There is sufficient evidence to indicate that the reaction is the result of hemolysis of the donor's incompatible red blood cells. A typical reaction is characterized by an immediate diminution in the output of urine (in instances of severe involvement, by complete suppression) and hemoglobinuria;[3] within a few hours a moderate degree of icterus appears; the nonprotein nitrogen content of the blood rises gradually and within a few days reaches a high level, and a progressive state

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1. Bordley, J.: Reactions Following Transfusion of Blood, with Urinary Suppression and Uremia, Arch. Int. Med. **47**:288 (Feb.) 1931.

2. (*a*) Stetson, R. E.: Causes and Prevention of Posttransfusion Reactions, S. Clin. North America **13**:319 (April) 1933. (*b*) DeGowin, E. L., and Baldridge, C. W.: Fatal Anuria Following Blood Transfusions: Inadequacy of Present Tests for Compatibility, Am. J. M. Sc. **188**:555 (Oct.) 1934. (*c*) Irsigler, F. J.: Urämie nach Bluttransfusion, Zentralbl. f. Chir. **58**:1682 (July 4) 1931. (*d*) Polayes, S. H., and Lederer, M.: Reactions to Blood Transfusion, J. Lab. & Clin. Med. **17**:1029, 1932. (*e*) von Deesten, H. T., and Cosgrove, S. A.: Renal Insufficiency Following Transfusion: Recovery After Venesection, Ann. Int. Med. **7**:105, 1933. (*f*) Johnson, R. A., and Conway, J. F.: Urinary Suppression and Uremia Following Transfusion of Blood, Am. J. Obst. & Gynec. **26**:255, 1933.

3. There is little doubt that hemolysis of red blood cells is responsible for the reaction, but accurate chemical and spectroscopic studies of the exact hemoglobin breakdown products which appear in the urine have not been mentioned in the available reports as far as we know.

of uremia develops. The uremia may end fatally, or the sudden onset of diuresis may be followed by rapid recovery. While it is not uncommon for chills, dyspnea or pain in the lumbar region to occur during the early part of the transfusion, these immediate symptoms may be absent.

In cases studied at necropsy a similar alteration in the kidneys has been seen, affecting various parts of the uriniferous tubule and associated with the precipitation of hemoglobin or its derivatives. Some observers [4] have found the lesion to be identical with that of patients with blackwater fever dying with urinary suppression. In about half the autopsies recorded focal necrosis was noted in the liver.

During the past six years about two thousand transfusions have been performed in the third medical and surgical divisions of Bellevue Hospital, during which time six reactions of incompatibility have occurred, making an incidence of approximately 0.3 per cent.

The seriousness of these reactions and the recent revival of interest in them have prompted us to report our experience in this regard.

REPORT OF CASES

CASE 1.—F. B., a white man aged 55, was admitted to Bellevue Hospital on July 31, 1930, with diffuse inflammation of the right foot. He was known to have had diabetes mellitus for years. The infection of the foot persisted and was complicated by gangrene of two toes and osteomyelitis. On August 16 the right foot was amputated, but the stump did not heal satisfactorily. On Jan. 2, 1931, the patient's temperature suddenly rose to 105 F. The blood pressure was 110 systolic and 60 diastolic. The urine was normal.

On January 5 the patient's blood was typed and found to belong in group 1 (Jansky). The donor's blood was not typed, but cross-matching indicated that there was no agglutination of the red blood cells with the patient's serum. On this day the patient was given 500 cc. of blood by the direct method. Fifteen minutes later he vomited and had a severe chill. Urinalysis on the same day showed protein 1+, a few red blood cells and a 4+ benzidine reaction. The next morning jaundice was noted. The output of urine was diminished to less than 5 ounces (150 cc.) for twenty-four hours. On the fourth day the nonprotein nitrogen content reached 150 mg. per hundred cubic centimeters of blood, and the output of urine was 10 cc. for twenty-four hours. On the sixth day the patient passed 3 cc. of urine. The nonprotein nitrogen content was 102 mg. per hundred cubic centimeters of blood. The patient died in coma on the seventh day following the transfusion. The donor's blood group was not determined, and cross-matching was not repeated after the transfusion.

Gross Postmortem Examination.—The body was that of a well developed and well nourished white man of about 50. The amputation stump of the right foot (at the metatarsophalangeal joint) showed slight suppuration of the edges. There were several irregular areas of ecchymosis from 1 to 3 cm. in diameter in the

4. Wakeman, A. M.; Morrell, C. H.; Eisenman, A. J.; Sprunt, D. L., and Peters, J. P.: The Metabolism and Treatment of Blackwater Fever, Am. J. Trop. Med. **12**:407 (Nov.) 1932. Dudgeon, L.: Blackwater Fever, J. Hyg. **19**: 208 (Oct.) 1920.

skin of the right leg. Limitation of the incision to the abdomen made examination of the thorax difficult. The serous sacs were free from fluid or adhesions. The heart and lungs were not removed, but small pieces of the lungs were taken for microscopic examination.

The spleen was enlarged, and its capsule was tense and smooth. It weighed 500 Gm. There were numerous punctate hemorrhages in the capsule. On section its pulp was soft and dark red, and it oozed blood. The follicles could not be seen.

The liver was enlarged, weighing 2,450 Gm. Its capsule was smooth, thin and glistening. On section there were prominent lobular markings. Focal areas were a light tawny yellow suggestive of fatty change. The surface was fairly firm. The gallbladder, bile ducts and portal vein were normal.

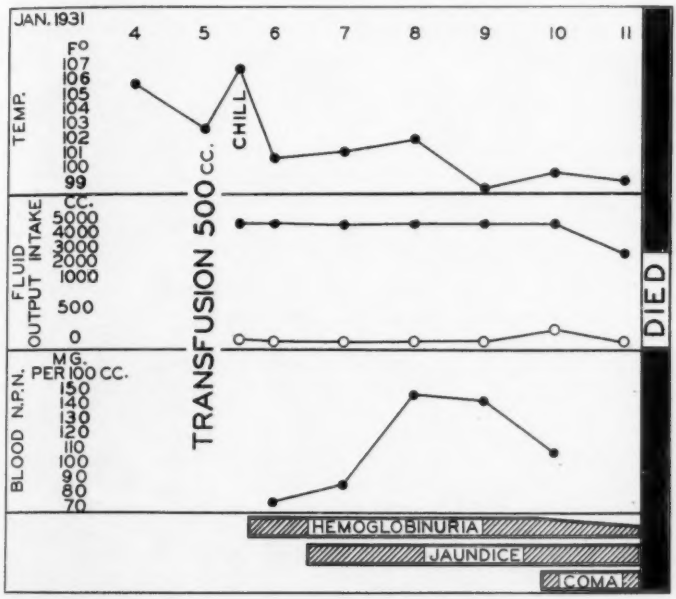

Fig. 1 (case 1).—F. B., a white man aged 55, had cellulitis of the foot. The patient's blood belonged in group 1 (Jansky). The donor's blood group was not determined, but cross-agglutination of the red blood cells with the patient's serum was negative before the transfusion. No recheck was made after the transfusion.

The pancreas and adrenal glands showed no visible changes. The appearance of the stomach and intestines was not remarkable.

The kidneys were enlarged, each weighing 235 Gm. The capsules stripped easily, leaving a fairly smooth, milk-gray surface. On section there was thought to be marked hyperemia of the medullary pyramids. The corticomedullary junction was sharply demarcated. The pelves, ureters and bladder showed no changes. The testes were normal in size and appearance.

Microscopic Postmortem Examination.—Sections of the lungs showed no inflammatory changes. Marked hyperemia and occasional areas of collapse were noted. There was moderate anthracotic pigmentation.

Liver: Sections from different areas of the liver showed similar lesions. There were scattered areas of necrosis in the lobules, tending to be central in location, sometimes involving the inner third of each lobule. In some of these areas there was hemorrhage. The adjacent hepatic cords were deeply pigmented by golden yellow and golden brown, highly refractive pigment. Kupffer's cells were filled and enlarged with deep black-brown pigment. There was a marked proliferation of fixed tissue cells in the periportal areas. Small numbers of plasma cells and leukocytes were present. There was no increase in the amount of connective tissue in these areas.

Spleen: There was marked hyperemia of the sinuses, with considerable hemosiderosis, both intracellular and extracellular. The splenic follicles were small, and the so-called germinal centers were not clearly visible. There was moderate arteriosclerosis.

Pancreas: Sections from the head of the pancreas showed no noteworthy changes.

Kidneys: Many blocks were taken from both kidneys, and they revealed a widely distributed alteration. Sections were stained with hematoxylin and eosin, the Van Gieson and the Weigert elastic tissue stain, the Gram-Weigert stain, and Mallory's phosphotungstic acid-hematoxylin stain. Sections were stained for reticulum by the method of Foot and Foot, for iron by the Perl method and the Turnbull method, for hemoglobin by the Lepehne method and the Brown method and for fat with sudan IV.

The glomeruli were not reduced in number and were intact except for focal thickening of the basement membrane and of the walls of the afferent arterioles. The loops were patent, as a rule, and contained erythrocytes. In some sections Bowman's capsule appeared distended, and there was an increase in the intracapsular space. However, many glomerular capsular spaces did not appear distended, and the capsule invested the contained tufts closely.

The medium-sized vessels showed no changes. The inner elastic layer was intact.

The interstitial stroma appeared edematous, with the tubules separated from each other by various intervals. This was most marked at the corticomedullary junction. In all sections there were focal areas exhibiting proliferation of histiocytes, plasma cells and a few polymorphonuclear leukocytes in the interstitial stroma as well.

Under low magnification what appeared at macroscopic examination to be medullary hyperemia was seen to be due to the presence of large reddish brown cystal masses precipitated in the collecting tubules and dilating their walls.

The tubules showed a severe regressive change. Their lumens appeared large, owing to desquamation or shrinkage of the lining cells or to distal obstruction.

Eosinophilic débris was seen to be free in the lumens of the proximal tubules. Farther down the tubule the cast formation encountered was remarkable. In the thin and thick portions of Henle's loop and the distal convoluted segment deeply eosinophilic droplets formed masses and casts. At first glance they appeared to be red blood cells, but comparison with the erythrocytes within the vessels near-by revealed that they were as a rule either much smaller or much larger, rarely the same size.

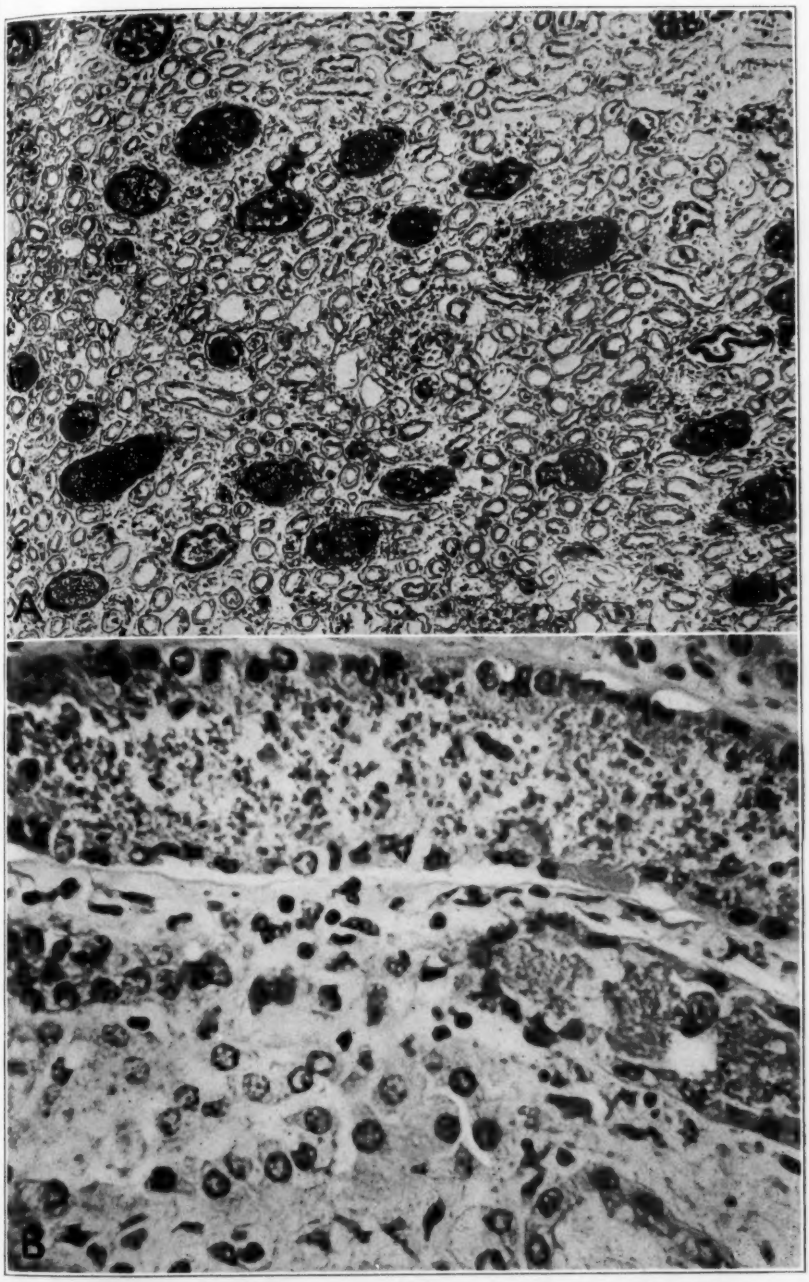

Fig. 2 (case 1).—*A*, a low power view of a section through the medulla of the kidney. Note the formation of large obstructing pigment masses of hematin crystals and granules. *B*, a high power photomicrograph showing in more detail the tubular degeneration, interstitial edema and peculiar granular casts.

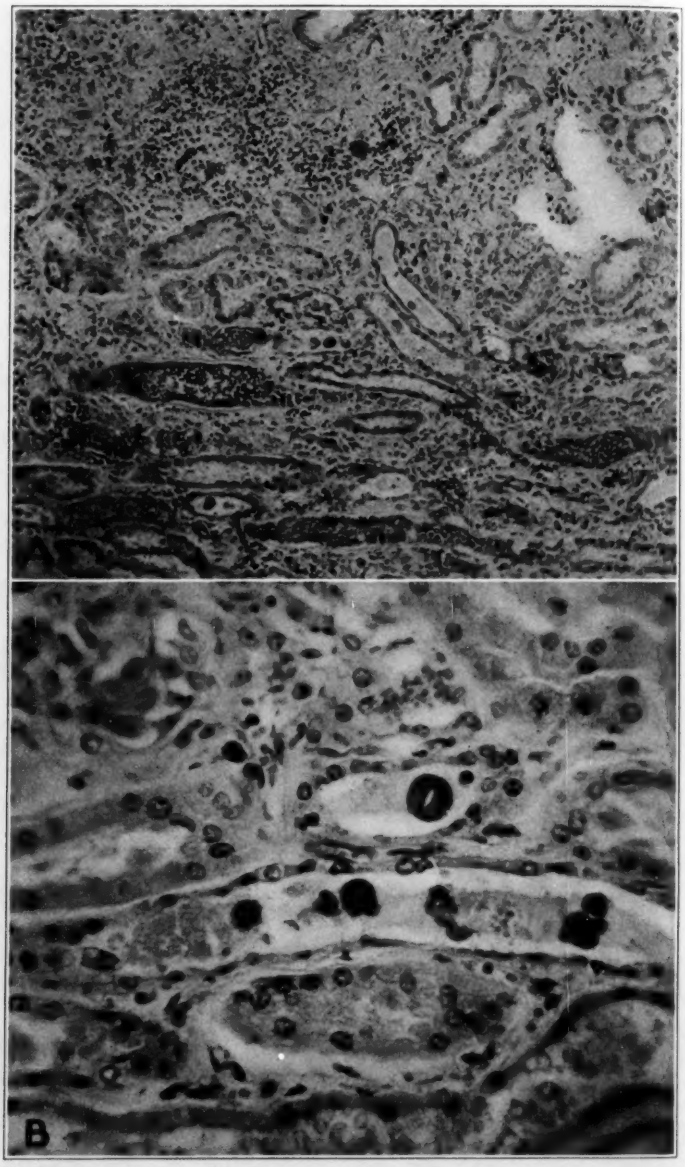

Fig. 3 (case 1).—*A*, a low power photomicrograph of a section through the cortex including a number of Henle loops, illustrating the interstitial edema, proliferation of fixed tissue cells, tubular dilatation and epithelial degeneration. The granular casts were abundant in segments of the Henle loops and the distal convoluted tubules. *B*, a high power photomicrograph of a section of the kidney, illustrating calcification in the Henle loops and a solitary miliary calculus in one tubule.

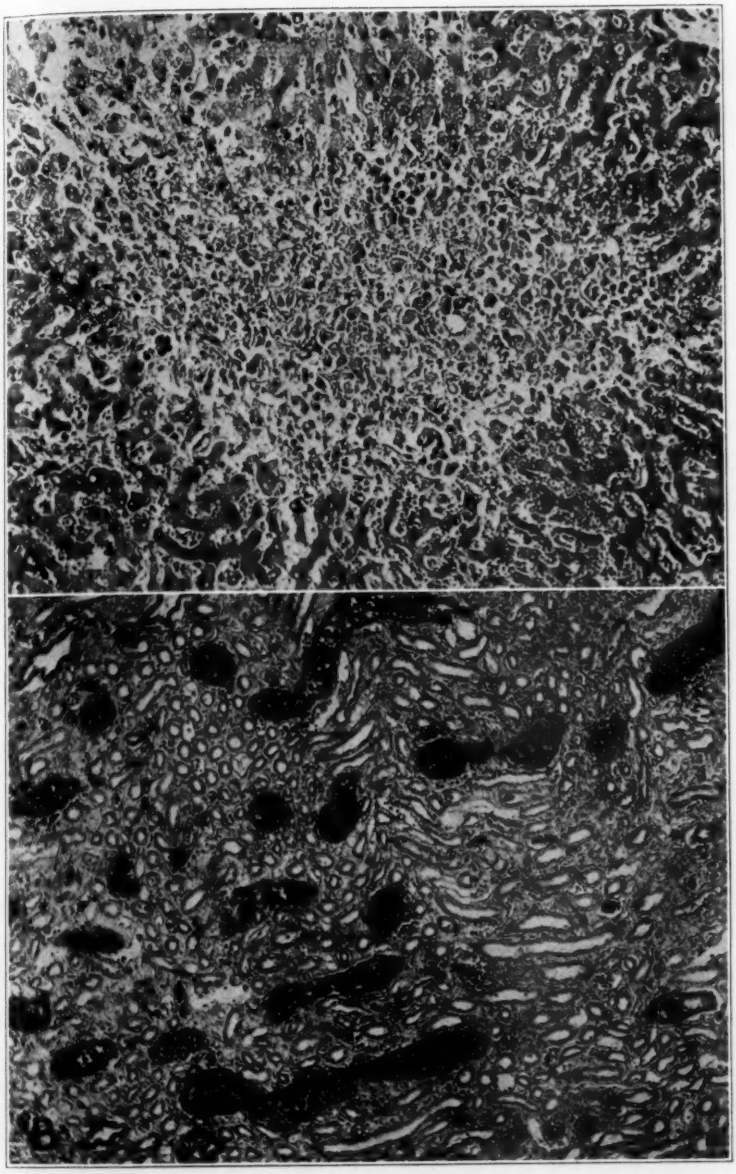

Fig. 4.—*A*, a low power photomicrograph of a section of the liver (case 1) illustrating the central focal necrosis. *B*, a low power photomicrograph illustrating the hematin granular masses obstructing the collecting tubules (case 4).

In some instances these droplets were coccoid. Sometimes they were discrete, and elsewhere they were seen embedded in a faintly eosinophilic matrix. This was best seen in sections stained with Mallory's phosphotungstic acid-hematoxylin stain.

Hemosiderin granules were seen in small numbers in the epithelium of the distal convoluted segments. The intact epithelium of the proximal and distal tubules showed various regressive changes, including loss of the outline of the cells, marked vacuolation of the cytoplasm and rarely a loss of nuclei. No intracytoplasmic eosinophilic granules were seen.

The most severe lesions were seen in the Henle loops. Almost all these loops contained granular casts composed of deeply eosinophilic particles or globules. In addition, in some there were casts of desquamated epithelial cells and tiny calcified masses, while others contained (new?) lining epithelial cells which were flattened, with small densely chromatinic nuclei. No mitoses were seen.

In the collecting tubules the casts were larger and brown (also in unstained sections) and were associated with marked dilatation and flattening of the lining cells (due to pressure atrophy). In places the cells were desquamated. The majority of the collecting tubules showed these casts. In some of the lining cells hemosiderin granules were present. Lepehne's stain,[5] which employs benzidine, was applied to paraffin sections, and the suspicion that the casts were composed of hemoglobin droplets was confirmed.

The red blood cells in the renal vascular bed showed no individual changes.

Stains for iron (the Perl and the Turnbull method) revealed that the casts contained no free iron. The only demonstrable pigment containing free iron was seen in the form of the hemosiderin granules previously noted.

Diagnosis.—The pathologic diagnosis was acute nephrosis, mild arteriolar nephrosclerosis, focal necrosis and hemorrhage of the liver, septic softening of the spleen and infection of the amputation stump of the right foot.

Case 2.—A. K., a Puerto Rican housewife aged 25, was admitted to the hospital complaining of vaginal bleeding for three days after attempted abortion. The past history was irrelevant.

The patient had marked secondary anemia. The blood pressure was 100 systolic and 70 diastolic. Urinalysis was not performed. The patient's blood belonged in group 1 (Jansky).

On July 9, 1932, a transfusion of 500 cc. of group 1 blood was given by the direct method, with no reaction. The next day 360 cc. of group 1 blood from another donor was given, with no unusual reaction. On August 6, a transfusion of 500 cc. of blood from a third donor, the patient's husband, was given. This donor's blood belonged in group 1 (Jansky). An hour and a half after the tranfusion the patient vomited and had a chill lasting for twenty-five minutes. Six hours later she complained of pain in the lower part of the back and difficulty in breathing. The pulse rate was 134, and the temperature was 105 F. Urinalysis at this time showed many red blood cells and protein 4+. The nonprotein nitrogen content of the blood was 75 mg. per hundred cubic centimeters. On August 8 jaundice was noticed for the first time, and vomiting began. The output of urine was 2 ounces (60 cc.) for this twenty-four hour period. On August 10 the nonprotein nitrogen content of the blood was 100 mg. per hundred cubic centimeters. Jaundice and vomiting persisted, and edema appeared on the face and over the sacral region. On August 17 the nonprotein nitrogen content of the

5. Lepehne, G.: Zerfall der roten Blutkörperchen beim Ikterus infestiosus (Weil): Ein weiterer Beitrag zur Frage des hematogenen Ikterus, des Hämoglobin- und Eisenstoffwechsels, Beitr. z. path. Anat. u. z. allg. Path. **65**:163, 1919

blood reached 180 mg. per hundred cubic centimeters. On August 20 the output of urine suddenly increased, and the patient recovered rapidly, being discharged on September 27. After the transfusion the regrouping of the bloods of the patient and donor by Dr. R. Stetson confirmed their identity as belonging to group 1 (Jansky).[6] The patient was reexamined on March 19, 1933. Urinalysis revealed no abnormality. The nonprotein nitrogen content of the blood was 38 mg. per hundred cubic centimeters.

Case 3.—J. C., a white man aged 42, was admitted to the hospital on July 22, 1930, because of a crushing injury of the left foot. His past history was unimportant. The blood pressure was 134 systolic and 85 diastolic. Urinalysis showed a specific gravity of 1.020, no protein, no sugar and a normal microscopic appearance. The blood belonged in group 1 (Jansky). The patient received 500 cc. of

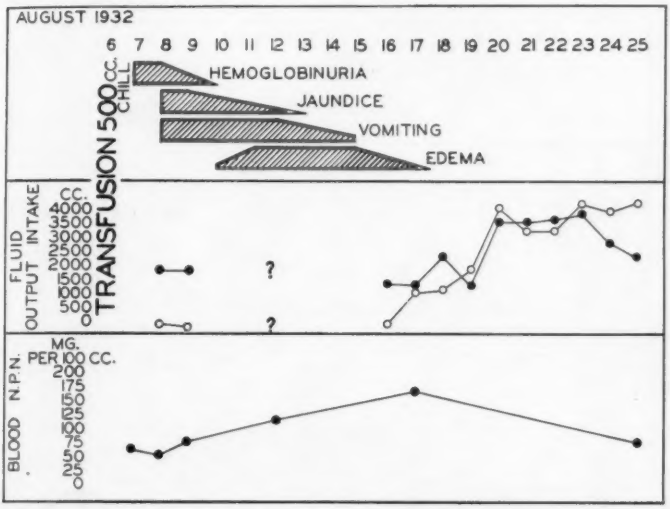

Fig. 5 (case 2).—A. K., a white woman aged 25, had a uterine hemorrhage and anemia. Her blood and the bloods of the three donors belonged in group 1 (Jansky). The results of cross-agglutination tests before the third transfusion were negative whereas following this transfusion there was difference of opinion (for a full discussion of this case see the article by Stetson [2a]). A reaction occurred after the third transfusion.

group 1 blood by the direct method on July 23 and also on July 25 from two different donors, with no reaction. On July 28 he received 500 cc. of blood from a third donor. During the transfusion the patient complained of weakness. Immediately after the transfusion he became cyanotic, perspired profusely and complained of being cold. An urticarial rash appeared on the arms and back. A chill developed which lasted for twenty-five minutes. One half hour after the transfusion the temperature was 105 F. The donor's blood was retyped and found to belong in group 2.

6. Full discussion of this case was published in a paper by Dr. Stetson.[2a]

Two hours after the transfusion the patient passed frankly red urine, containing no red blood cells. The benzidine reaction was strongly positive. The nonprotein nitrogen content of the blood was 70 mg. per hundred cubic centimeters. Vomiting began that evening. The next morning jaundice appeared. The urinalysis showed protein 4+, numerous red blood cells, white blood cells and hyaline and granular casts. The output of urine was greatly diminished. The patient's condition became progressively worse. On August 11, two weeks after the transfusion, the nonprotein nitrogen content of the blood reached 520 mg. per hundred cubic centimeters. The patient was stuporous and dehydrated, and there were fibrillary twitches of the facial muscles. On August 12 he had several clonic convulsions. There was no edema. On August 16 bilateral nonsuppurative

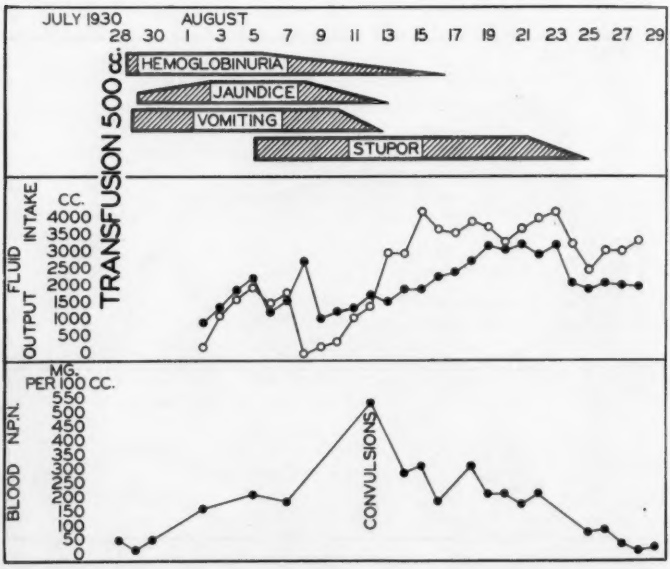

Fig. 6 (case 3).—J. C., a white man aged 42, had anemia due to loss of blood from an injury to one foot. The patient's blood belonged in group 1 (Jansky); the third donor's blood proved to belong in group 2. A reaction occurred after the third transfusion.

parotitis developed which resolved after six days. On August 13 there was a sudden increase in the output of urine. Afterward the output of urine continued high, and the nonprotein nitrogen content gradually fell. Vomiting ceased, and the patient's mental state returned to normal. He was discharged improved on September 19. The nonprotein nitrogen content of the blood had returned to normal, but urinalysis still showed a trace of protein, many red blood cells and many hyaline casts. Impairment of the maximum concentrating power was persistently marked. Reexamination on Feb. 2, 1932, showed that the concentrating power was normal. Urinalysis was normal.

Case 4.—T. C., a Puerto Rican housewife aged 24, was delivered of a normal child at term on Dec. 30, 1930. Evidence of postpartum pelvic inflammation developed. There were repeated chills, and the temperature rose to 104 F. On Jan. 3, 1931, urinalysis was normal. The blood belonged in group 1 (Jansky). A group 1 donor was selected. On direct matching there was no agglutination of the donor's red blood cells after twenty minutes. On January 5 the patient was given 400 cc. of blood by the direct method. A few hours later frankly red urine which contained hemoglobin was passed. The next morning jaundice was noted. The output of urine was less than 3 ounces (90 cc.) a day for the rest of the course. On January 8 the nonprotein nitrogen content of the blood was 110 mg. per hundred cubic centimeters. Edema did not develop. The patient became

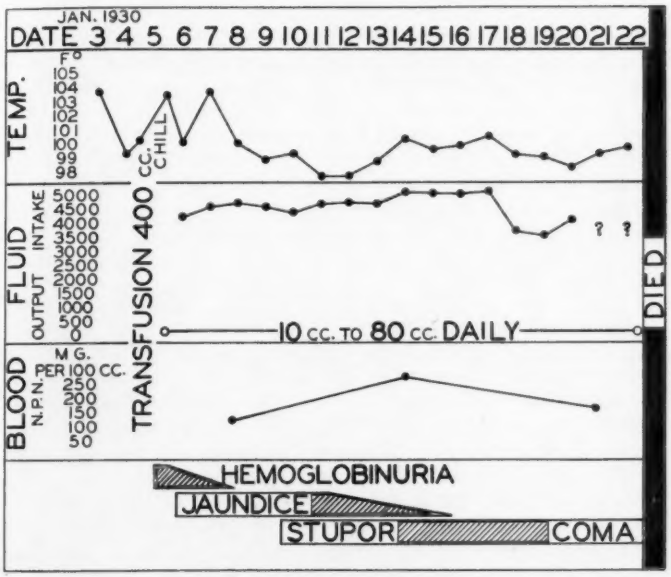

Fig. 7 (case 4).—T. C., a white woman, aged 24, had postpartum sepsis. Her blood belonged in group 1 (Jansky). The donor's blood proved to belong in group 2. Cross-agglutination before the transfusion was reported as negative.

stuporous and dehydrated. The nonprotein nitrogen content of the blood rose to 245 mg. per hundred cubic centimeters and subsequently fell to 180 mg. Urinalysis showed protein 4 + and innumerable red blood cells. A pelvic abscess developed on January 21 which required incision and drainage. The patient remained stuporous and died on January 24. Retyping of the donor's blood showed it to belong in group 2.

Gross Postmortem Examination.—The body was that of a well developed white woman in a fair state of nutrition. There was moderate generalized subcutaneous edema. There was an operative incision about 10 cm. long in the right

lower quadrant of the abdomen held together by several deep sutures. A long rubber dam drain protruded through the incision, and on it was a small amount of thin yellow purulent fluid.

The peritoneum was everywhere dull and covered with a creamy purulent exudate. There was a large amount of light greenish yellow fluid free in the cavity. The small intestines were loosely matted together and considerably distended. Flakes of fibrin could be brushed off the serous surfaces of the intestines.

The pleural and pericardial sacs were free from fluid or adhesions.

The lungs were crepitant throughout. Considerable edema and hyperemia were noted in the lower lobes in their dependent portions. No areas of consolidation could be made out. The bronchi contained frothy fluid.

The heart was not enlarged, weighing 250 Gm. There were no visible changes in the endocardium, valves, myocardium or epicardium. The coronary vessels were normal. The aorta was normal throughout its length.

There were no visible changes in the gastro-intestinal tract, except for the fibrinous exudate on the serous surface.

The liver was slightly enlarged, weighing 1,550 Gm. The capsule was not thickened and was altered only by the fibrinous exudate on the surface. On section the lobular markings were not accentuated. The surface was grayish brown.

The gallbladder, bile ducts and portal vein were normal.

The pancreas and the adrenal glands were normal.

The spleen was slightly enlarged and weighed 270 Gm. Its capsule was smooth. On section the organ was soft and purplish red, and the follicles could not be made out. The splenic artery and vein were patent.

Both kidneys were enlarged and were embedded in a moderate amount of fat. On section, the capsule came away easily, leaving a smooth, moist surface which was mottled grayish red. The cortex was slightly swollen and pale gray, while the medulla appeared hyperemic. In the medullary region of the right kidney grayish white streaks extending into the tips of the papillae were distinctly seen. In places these streaks could be seen in the cortex. The whole cut surface of the right kidney presented a swollen, ill defined appearance. The pelvis of the right kidney was markedly hyperemic and contained purulent urine.

On section of the left kidney the cortical-medullary junction was sharp. The medullary pyramids appeared markedly hyperemic. The pelvis and ureter were free from inflammatory changes and contained no pus. The bladder when opened was seen to be contracted; the lining was diffusely hyperemic and in places was covered with a gray, necrotic membrane.

The uterus was slightly enlarged and somewhat boggy in consistency, although the myometrium was of normal thickness. The right tube and ovary were enlarged, matted together, covered with a purulent exudate and plastered on the fundus of the uterus. On section the right ovary was about three times the normal size, and was the seat of multiloculate abscesses. The fallopian tube on this side also was thickened and adherent to the ovary. Its lumen contained the same type of thick greenish yellow pus. The right broad ligament was the seat of a large abscess containing greenish yellow pus. This extended into the pouch of Douglas, which was filled with pus. The endometrium was hypertrophied and on one side presented an area of marked edema. The cervix was soft, the os admitting one finger. The vagina showed nothing unusual.

The head was not examined.

Microscopic Postmortem Examination.—Sections of the myocardium revealed no significant changes. There was moderate fiber and nuclear hypertrophy.

Lungs: There were patchy areas of collapse and areas of pulmonary edema. In one section there were areas of hemorrhage and a fine network of fibrin in the alveolar spaces. There were no inflammatory changes in the bronchi.

Spleen: The malpighian bodies were of normal size. So-called germinal centers were not present. There was moderate arteriosclerosis. The venous sinuses were prominent and gorged with blood. Pulp cells were prominent.

Liver: There were focal areas of fatty change and some loss of staining power. No hemorrhages were seen. Kupffer cells were not particularly prominent. The bile ducts showed no changes.

Kidneys: Section of the right kidney was complicated by the presence of a marked, diffuse suppurative process with particular involvement of the medulla. In this section, however, there were, in addition, blood casts of various types. Sections of the left kidney showed none of the suppurative process seen in the right kidney. A widespread degenerative tubular lesion and moderate edema of the interstitial stroma were noted.

Under low magnification the collecting tubules could be seen to be overdistended and plugged with large brown casts. These were likewise brown in unstained sections. In places the tubules were free from such casts, but even in these tubules the lining epithelium was desquamated in places or exhibited various regressive changes, consisting of a loss of the outline of the cells and nuclei and some granular degeneration. There was marked vacuole formation in the intact tubules. The glomeruli were normal in size and number. They exhibited no individual changes of any note. The blood vessels and arterioles particularly were well preserved.

Elsewhere the uriniferous tubules, particularly in Henle's loop and the distal convoluted segment, showed various stages of a degenerative process. In some the lining epithelium was completely desquamated; in others, it was replaced by flattened epithelium and pyknotic nuclei. In others the epithelium merely showed a loss of nuclei. In all these units there was marked formation of casts composed of deeply eosinophilic masses. In places these masses were discrete; elsewhere they were embedded in an albuminous mass. The droplets varied in size from coccoid granules 1 or 2 microns in diameter to droplets larger than a red blood cell. Deeper in the uriniferous tubule the casts changed from deep red to reddish brown in the collecting tubules. In unstained sections these casts and the convoluted tubules had a faint reddish brown tinge, whereas in the collecting tubules they were definitely brownish. Stains for iron revealed practically no free iron in these casts or in the epithelium lining the tubules. Lepehne's [5] stain confirmed the impression that the casts contained hemoglobin.

Uterus and Ovary: Section of the wall of the uterus and ovary showed a diffuse suppurative exudate on the surfaces, with moderate, fixed tissue proliferation and granulation tissue at the base of the exudate.

Diagnosis.—The pathologic diagnosis was acute nephrosis, abscess of the right ovary and tube, generalized peritonitis, focal fatty changes of the liver, ascending acute suppurative pyelonephritis on the right side, anasarca, congestion and hyperplasia of the pulp of the spleen, focal collapse of the lungs, emphysema and pulmonary edema.

Case 5.—A. H., a white woman aged 25, was delivered of a normal full term infant on Dec. 29, 1933. One hour after delivery she complained of a severe, sharp pain in the left side of the chest and presented the picture of shock. A diagnosis of pulmonary embolism was made. Blood transfusion was suggested, and since the patient appeared moribund, time was not taken to determine the blood group of the donor, the patient's husband. Direct matching of the bloods showed no gross agglutination. After 220 cc. of blood had been transfused by the direct method the patient suddenly became dyspneic and roused sufficiently to complain of choking. The transfusion was stopped. On the following day the patient passed 9 ounces (300 cc.) of frankly red urine, containing hemoglobin.

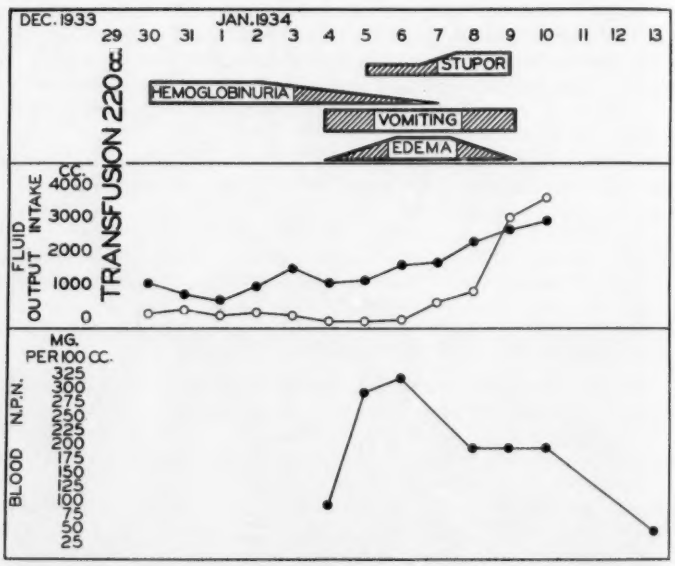

Fig. 8 (case 5).—A. H., a white woman aged 25, had postpartum pulmonary embolism with shock. The patient's blood belonged in group 1 (Jansky). The donor's blood proved to belong in group 2. There was no cross-agglutination before the transfusion was given.

The oliguria and hemoglobinuria persisted for the next seven days. During this period the patient was in a semistuporous state and vomited continually. The nonprotein nitrogen content of the blood had risen to 315 mg. per hundred cubic centimeters and the creatinine content to 8.8 mg. Generalized edema appeared on the sixth day following the transfusion and disappeared on the eleventh day. There was no jaundice. On the eleventh day following the transfusion diuresis set in suddenly. Thereafter recovery was continuous and rapid. The patient was discharged on Jan. 13, 1934. Retyping at that time showed that the patient's blood belonged to group 1 (Jansky) and that of the donor to group 2.

CASE 6.—M. G., a white woman aged 24, entered the hospital on Feb. 14, 1929, complaining of profuse vaginal bleeding for three weeks. The temperature was normal. Urinalysis showed no protein, sugar or formed elements. The Wassermann reaction of the blood was negative. The red blood cell count was 3,970,000 and the hemoglobin value 65 per cent. The blood belonged to group 1 (Jansky). On February 21 the patient was given a transfusion, her husband acting as donor. His blood belonged in group 1 (Jansky), and cross-matching of the red cells with the patient's serum showed no agglutination. The direct method of transfusion was used. After 110 cc. of blood had been given the patient suddenly became dyspneic and complained of "choking." The transfusion was halted for a few minutes, and the symptoms subsided. The transfusion was then resumed until a total of 400 cc. of blood had been given, when the patient again complained of choking and became dyspneic. The transfusion was stopped. A few hours later the patient vomited but had no other complaint. The next morning vomiting reappeared, and distinct jaundice was noticed. On this day (February 28) the patient passed no urine. The nonprotein nitrogen content of the blood was 150 mg. per hundred cubic centimeters. The following day she voided ½ ounce (15 cc.) of dark brown urine containing hemoglobin, many red blood cells and protein. For the following ten days the output of urine was 6½, 8, 8, 8, 8, 9, 12½, 10, ? and 3 ounces (200, 240, 240, 240, 240, 270, 475, 300, ? and 90 cc.), respectively. Protein red blood cells and casts persisted throughout. Hemoglobin was present in all but the last sample of urine collected. Vomiting persisted throughout. The patient passed into a stuporous state, and although no further chemical studies of the blood were made, bedside notes described her as presenting the symptoms of a typical uremic state. She died on March 7, the fourteenth day after the transfusion. There was no rechecking of the blood groups or cross-matching. Permission for necropsy was not obtained.

CASE 7.—E. H., a Puerto Rican housewife aged 24, entered the hospital on May 1, 1935, complaining of pain in the lower part of the abdomen and vaginal bleeding of one week's duration. A diagnosis of bilateral salpingitis and possible ectopic pregnancy was made. The blood pressure was 86 systolic and 56 diastolic. The urine showed albumin, a few clumped white blood cells, a specific gravity of 1.015, 3,300,000 erythrocytes and 55 per cent hemoglobin. The patient was given palliative treatment, and on May 12 left the hospital at her own request.

Three days later the patient returned to the hospital, complaining of pain in the lower portion of the abdomen and vaginal bleeding. The blood pressure was 94 systolic and 60 diastolic. The urine again showed albumin, a few clumped white blood cells and a specific gravity of 1.020. The left ankle became painful and swollen, a condition diagnosed as gonococcic arthritis. On May 22 the patient was given a transfusion of 500 cc. of blood, her husband acting as donor. The bloods of the patient and donor belonged in group 1 (Jansky). During the transfusion the patient stated that she felt "funny," but she was not short of breath and she had no choking sensation or pain in the back. A severe chill developed, which was followed by a rise in temperature to 106 F. Dark urine was passed a few hours later. The following day jaundice was noticed. The output of urine diminished to 15 cc. on the second day and to 8 cc. on the third day. The nonprotein nitrogen content of the blood rose to 60 mg. per hundred cubic centimeters on the fifth day and reached 150 mg. on the eighteenth day. For the first ten days the patient vomited everything taken by mouth. The specific gravity of the urine remained fixed at a level of from 1.008 to 1.012. Infusions and clyses of a 5 per cent solution of dextrose in saline solution were given daily. The output

of urine reached 900 cc. on the seventh day. On June 1 the patient became generally edematous, and the parenteral administration of fluid was discontinued. The edema disappeared in three days. Gradual and uneventful recovery followed the onset of diuresis. The bloods of the patient and donor were retyped and were shown to belong in group 1 (Jansky). There was no agglutination of the donor's red blood cells by the patient's serum or of the patient's red blood cells by the donor's serum.

On June 13 a test of the renal function showed fixation of the specific gravity and a 10 per cent excretion of phenolsulfonphthalein in two hours as evidence of the severe impairment of the renal function.

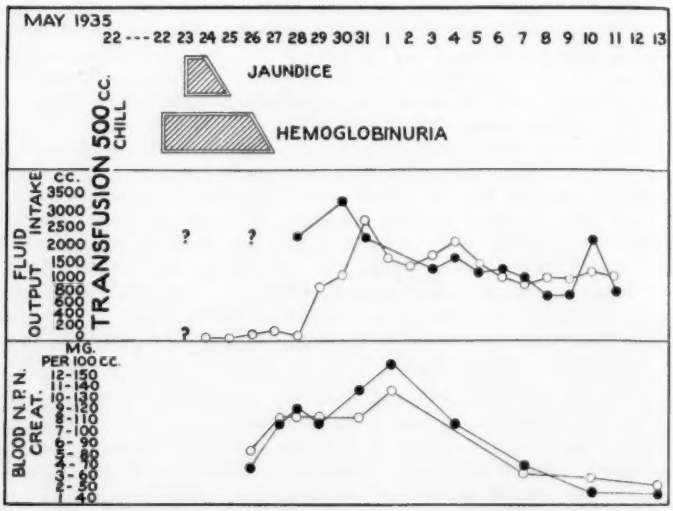

Fig. 9 (case 7).—E. H., a white woman aged 24, had uterine bleeding and anemia. Her blood belonged in group 1 (Jansky), as did also the donor's. A recheck of the blood groups and cross-agglutination after the transfusion confirmed these findings.

COMMENT

The accompanying table gives a summary of the clinical observations in this series. The bloods of all the recipients belonged in group 1 (Jansky). In three instances the reaction followed a transfusion of group 2 blood; in two cases the failure to recheck the blood groups after the transfusion was given left doubt as to the classification; in two cases retyping after the transfusion confirmed the fact that the blood of both the donor and the recipient belonged to group 1 (Jansky).

Alarming symptoms appeared during the transfusion in two cases, no subjective symptoms appeared in three cases and in the remaining two cases the subjective symptoms were vague and were not considered of sufficient importance to warrant the discontinuance of the transfusion.

Summary of the Clinical Data

Patient	Sex	Age	Diagnosis	Blood Group (Jansky)		Transfusion of Blood, Cc.*	Reaction During Transfusion	Climax Reached, Day	Result	Comment
				Recipient	Donor					
F. B.	M	55	Cellulitis of foot	1	?	500	None	7	Died	One transfusion; vomiting 15 minutes later; donor's blood group not determined; cross-matching not repeated after transfusion; necropsy
A. K.	F	25	Uterine hemorrhage; anemia	1	1	500	None	14	Recovered	Three transfusions with different donors; 1½ hours after third transfusion vomiting, chill, dyspnea and pain in lumbar regions; recheck after transfusion confirmed blood grouping †
J. C.	M	42	Crushing injury to foot with hemorrhage; anemia	1	2	500	Weakness	16	Recovered	Three transfusions with different donors; immediately after third transfusion, chill lasting for 25 minutes, cyanosis and diffuse urticarial rash; one half hour later, temperature of 105 F.
T. C.	F	25	Postpartum sepsis; pelvic abscess	1	2	400	None	19	Died	One transfusion; death 3 days after drainage of pelvic abscess; necropsy
A. H.	F	25	Shock following postpartum pulmonary embolization	1	2	200	"Choking" sensation; dyspnea	11	Recovered	One transfusion
M. G.	F	24	Incomplete abortion; anemia	1	1 ?	400	"Choking" sensation; dyspnea	14	Died	One transfusion; blood groups and cross-matching not rechecked after transfusion
T. H.	F	24	Incomplete abortion; anemia	1	1	500	"Funny" feeling	7	Recovered	One transfusion; recheck of blood groups proved that bloods of donor and recipient belonged in group 1 (Jansky) and that there was no cross-agglutination

* In all instances the direct method was used.
† See Stetson [2a] for detailed discussion of this case.

There appeared to be no striking relationship between the amount of blood transfused and the severity of the reaction. Two patients who received 400 cc. died, whereas three patients who received 500 cc. recovered. Furthermore, patient A. H., who received 200 cc., had a more severe and protracted course than patient E. H., who received 500 cc. Death occurred on the seventh and the fourteenth day, respectively, in two cases and on the nineteenth day in the case of the patient who was operated on for a complicating pelvic abscess.

A prompt and marked diminution in the output of urine occurred in every instance. The longest duration of marked oliguria before the onset of diuresis and recovery was sixteen days. Slight but distinct icterus appeared in five of the seven patients and lasted for from five to fourteen days. When some urine was voided directly after the transfusion it invariably contained what was believed to be hemoglobin or its derivatives. The blood pressure was not elevated, and generalized edema appeared in two patients, but only after infusion of large amounts of saline and dextrose solutions.

The mechanism by which incompatible blood produces structural and functional damage of the kidneys and the hepatic lesions noted in some fatal cases is not clear. Bordley considered various explanations in his study. He said he felt that mechanical blockage of the renal tubules by the hemoglobin and hematin casts could not be held entirely accountable, though this view is held by some. He stated that the weight of evidence suggested that the anatomic and functional renal changes were produced by an unknown toxin resulting from the mixing in vivo of incompatible bloods. That hemoglobin itself may not produce anatomic or functional changes in the kidney was previously shown by Sellards and Minot [7] and by Bayliss.[8]

The necrosis of the liver noted in one of our fatal cases and in numerous other reports of necropsies is considered by some to be analogous to necrosis seen in other toxic states, for example, eclampsia. In view of the manifest relation to a hemolytic reaction, we wish to call attention to the extensive studies of Pearce [9] (1904-1906), in which he

7. Sellards, A. W., and Minot, G. R.: Injection of Hemoglobin in Man and Its Relation to Blood Destruction, with Especial Reference to the Anemias, J. M. Research **34**:469, 1916.

8. Bayliss, W. M.: Is Haemolysed Blood Toxic? Brit. J. Exper. Path. **1**:1 (Feb.) 1920.

9. Pearce, R. M.: The Experimental Production of Liver Necroses by the Intravenous Injection of Hemagglutinins, J. M. Research **12**:329 (July) 1904. Pearce, R. M., and Winne, C. K., Jr.: Concerning Hemagglutinins of Bacterial Origin and Their Relation to Hyalin Thrombi and Liver Necroses, Am. J. M. Sc. **128**:669, 1904. Pearce, R. M.: A Further Study of the Experimental Production of Liver Necroses with Injection of Hemagglutinative Sera, J. M. Research **14**:541, 1906.

dealt with identical hepatic necrosis induced in experimental animals by the the injection of serums rich in hemagglutinins. He believed that the lesions he observed were secondary to impaction of agglutinated red blood cells (with the formation of hyaline thrombi) in the hepatic sinusoids, shutting off the blood supply. These lesions were so easily produced and of such severity that he was able to use the method to induce a form of experimental cirrhosis.[10]

While the ultimate cause of some of the manifestations must be considered as still unexplained, there can be little doubt that the syndrome is initiated by hemolysis of the donor's red blood cells. There is a striking similarity to the suppression of urine and uremia seen in cases of severe blackwater fever,[4] even with regard to the histopathologic changes in the kidneys.

Bordley [1] stated: "In not a single case is there complete and satisfying evidence to prove that the blood of the donor was compatible with that of the recipient." In this regard he especially stressed the necessity for repetition of the cross-matching after the reaction has occurred. A review of our data and other recent reports [11] indicate that in some instances retyping and recross-matching failed to show any evidence of incompatibility. It seems from this that in rare instances serious hemolytic reactions may be unavoidable in the present state of knowledge of blood groups.

Our pathologic studies confirm the observations of Bordley and others and shed no new light on the problem of the pathogenesis of the lesions. It is worth reiterating that the essential lesions consist of tubular dilatation and some degeneration (particularly affecting the epithelium of Henle's loop and the distal convoluted tubule) with interstitial edema, a picture suggestive of mercurial nephrosis. The degree of tubular damage observed varies with the time of death. The distinctive feature is the formation of peculiar obstructing pigment casts in the distal tubular segments.

The changes observed in the tubules in both our fatal cases apparently represented late stages in the events following a hemolytic reaction.

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10. Pearce, R. M.: Experimental Cirrhosis of the Liver, J. Exper. Med. **8**: 64, 1906.

11. Parr, L. W., and Krischner, H.: Hemolytic Transfusion Fatality with Donor and Recipient in the Same Blood Group, J. A. M. A. **98**:47 (Jan. 2) 1932. Wildegans, H.: Die Todesfaelle nach Bluttransfusionen, Deutsche med. Wchnschr. **56**:2031 (Nov. 28) 1930. Stewart, S. G.: Acute Renal Insufficiency Following Blood Transfusion, M. Clin. North America **15**:553, 1931. McCandless, H. G.: A Hemolytic Blood Transfusion Reaction with Oliguria, J. A. M. A. **105**:952 (Sept. 21) 1935. DeGowin and Baldridge.[2b] Irsigler.[2c] Polayes and Lederer.[2d] von Deesten and Cosgrove.[2e] Johnson and Conway.[2f]

The first patient came to necropsy seven days after the transfusion had been given, and the finding of calcific casts in the renal tubules recalls similar changes in the advanced stages of mercurial nephrosis. The second patient died seventeen days after a transfusion, and while the presence of suppuration elsewhere may have played a rôle in the degenerative epithelial changes seen the persisting pigment casts are evidence of the effect of the hemolytic reaction.

The location of the peculiar casts in cases like these suggests that concentration of the urine and an increase in the hydrogen ion concentration at this point in the uriniferous tubule lead to precipitation of the hemoglobin and injury to the epithelial cells. Beyond Henle's loop the breakdown of hemoglobin continues with the formation of large, obstructing crystal masses of hematin, some embedded in epithelial and amorphous débris, causing dilatation of the tubules. This explanation was first suggested by Baker and Dodds [12] in their clinical and experimental observations. Studying the effects of hemoglobinuria in rabbits, they found that since the normal rabbit's urine is alkaline, no anatomic changes developed, nor were hemoglobin or hematin casts formed in the tubules. However, when the urine was rendered acid, the breakdown of hemoglobin could proceed, and lesions identical with those seen in the kidneys in blackwater fever or in posttransfusion nephrosis were demonstrated.

We have concluded that the peculiar eosinophilic casts present in the convoluted tubules and in the Henle loops contain hemoglobin or one of its degradation products, because of the color of these casts in unstained sections and their positive reaction with benzidine by Lepehne's [5] method for staining hemoglobin in histologic preparations.

CONCLUSIONS

Observations are reported on seven patients who sustained a severe hemolytic reaction following transfusion with incompatible blood; four recovered, and three died.

The reaction was characterized by the sudden onset of oliguria (in instances of severe involvement, anuria) and hemoglobinuria and the gradual development of renal insufficiency and uremia.

Mistakes in grouping accounted for the reaction in three patients: in two, failure to recheck the grouping after the transfusion left doubt as to the classification; in two, regrouping showed the bloods of the donor and recipient to be of the same group. In the latter two patients the reaction was unpredictable and therefore, in the present state of

12. Baker, S. L., and Dodds, E. C.: Obstruction of the Renal Tubules During the Excretion of Haemoglobin, Brit. J. Exper. Path. **6**:247, 1925.

knowledge of blood groups and methods for their identification, must be considered unavoidable.

Pathologic observations in two of the three fatal cases revealed a necrotizing process affecting the uriniferous tubules which was like that seen in mercurial nephrosis. Distinctive pigment casts containing hemoglobin or its derivatives were conspicuous, and interstitial edema increased the size of the kidneys. Central focal necrosis was observed in the liver of one patient.

HYPERPARATHYROIDISM COMPLICATED BY HYPERTHYROIDISM

REPORT OF A CASE

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Hyperparathyroidism, long recognized as osteitis fibrosa cystica of von Recklinghausen, has become a well recognized clinical entity. Through the researches of such investigators as Hunter [1] and Jaffe,[2] stimulated by the observations of Mandl,[3] and from the numerous reports that have been published, the usual manifestations of this disease are now common knowledge to the clinician. The onset of the condition is insidious, and the symptomatology is so vague that until recently in most instances the patient with hyperparathyroidism has gone with the condition undiagnosed for many years. The clinical diagnosis is made, as a rule, only after the development of bony deformities or pathologic fractures. The case presented here is no exception to the rule, but because of certain unusual features it seems worthy of being reported.

The unusual features in this case were the associated hyperthyroidism, the rapid development of the clinical picture and the almost complete restoration of the atrophied bone, together with complete recovery after the removal of a parathyroid adenoma.

REPORT OF CASE

History.—The patient, an unmarried woman aged 33, was admitted to the Ancker Hospital on May 19, 1933, complaining of a fracture of the right wrist which was sustained after a trivial injury. An x-ray plate of the wrist had been made by the family physician, and he had referred her to the hospital because of the peculiar atrophy of the bones of the wrist and forearm which was revealed. The patient stated that she had not been entirely well since an attack of acute cystitis in 1931. In August 1932 she had an attack of abdominal pain with jaundice which was diagnosed as due to acute cholecystitis. She recovered from this attack after

From the Ancker Hospital, St. Paul, the Department of Medicine and the Department of Pathology, the University of Minnesota, Minneapolis.

1. Hunter, D.: Lancet **1**:897, 1930.

2. Jaffe, H. L.: Hyperparathyroidism (Recklinghausen's Disease of Bone), Arch. Path. **16**:63 (July) 1933.

3. Mandl, F.: Zentralbl. f. Chir. **53**:260, 1926; quoted by Hunter.[1]

an illness of about a month, with only residual fatigability. In November 1932 pain began to develop in the calves of the legs, and weakness was noted in the lower extremities. These symptoms did not respond to symptomatic treatment. In January 1933 the patient consulted a dentist, who advised the extraction of several teeth. While this was being carried out, a large piece of the alveolar process of the mandible came away with the teeth. The dentist recognized the abnormal condition of the bone and advised the patient to consult a physician. She continued to work, however, until May 19 when she sustained a fracture of the wrist and forearm. During the period between January and May the pains in the legs and the weakness had become progressively worse, and the patient was conscious of an unnatural irritability. Her weight in 1931 was 145 pounds (66 Kg.), and she considered this to be normal. When admitted to the hospital she weighed 116 pounds (52.6 Kg.).

The patient had a tonsillectomy in 1914. In 1918 she was acutely ill with influenza, and the following year she had a febrile illness of six weeks' duration which was diagnosed as due to endocarditis. In 1923 a tuberculous appendix was removed. The patient was subject to repeated acute infection of the respiratory tract.

Examination.—Physical examination showed the patient to be normally developed. She was intelligent and cooperative. There was evidence of a loss of weight, and the skin and mucous membranes were notably pale. There was no lymphadenopathy. The mouth was edentulous; the alveolar processes were larger than normal, but the mucous membrane over them was intact. There was a small, tender swelling over the eighth rib on the left side in the anterior axillary line. The heart and lungs were essentially normal. The blood pressure was 180 systolic and 110 diastolic. Examination of the abdomen revealed no abnormality but an appendectomy scar. The reflexes were hyeractive, but the muscle tone was poor. There was definite diminution of muscular irritability to electrical stimulation. The Colles fracture had been well reduced and immobilized. There was a diffuse swelling over the middle third of the left tibia.

Roentgenologic examination of the skeleton in May 1933 showed marked osteitis fibrosa cystica involving all the bones. The process was most pronounced in the left forearm, the long bones of the lower extremities, the ribs and the skull. The most advanced lesions were seen in the bones of the left forearm, where there was a pathologic fracture of the lower end of the radius. Both the radius and the ulna showed marked generalized decalcification of a coarse, irregular type. This was most pronounced at the site of the fractures in the left forearm and in the middle third of the left radius, where there was cystic expansion of the cortex. The periosteum of these bones was thickened and calcified. On June 17 a roentgenogram of the same region showed the decalcification to be much more advanced. In the carpal bones a similar process of decalcification, which had not been previously seen, was demonstrated. On July 10 further resorptive changes of the left radius and ulna were noted. The cystic area of the radius showed almost no calcium, and the cyst had increased in size (fig. 1). Many of the ribs showed decalcified, fusiform cystic swellings (fig. 2). The skull was thicker than normal, but both the inner and the outer table were thinned out, the cancellous portion of the bone showing an irregularly mottled appearance. At several points regular, almost circular cystic defects were seen in the skull (fig. 3). The tibias and fibulas showed an advanced degree of decalcification, which was fairly well limited to the shafts of the bones. The periosteum of these bones showed the

most marked involvement (fig. 4). The same process was seen in the femurs, but here the lesion was limited to the middle third of the bone. The pelvis and spine showed the least involvement.

The flat bones are said (Jaffe[2]) to be involved more frequently than the short tubular bones, but in this case the pelvis showed less involvement than the metacarpal bones.

TABLE 1.—*Laboratory Data*

Date	Blood Calcium, Mg. per 100 Cc.	Blood Phosphorus, Mg. per 100 Cc.	Calcium in Urine, Gm. in 24 Hrs.	Hemoglobin, %	Erythrocytes	Leukocytes	Blood Sedimentation, Min.
5/28/33	18.0	...	.....	60	3,300,000	12,500	101
6/ 1/33	16.5	...	0.980	..	.....	.....	...
6/ 2/33	....	3.6	0.150	..	.....	.....	...
6/ 3/33	....	...	0.200	..	.....	.....	...
6/ 5/33	....	...	0.430	..	.....	.....	...
6/ 6/33	....	...	0.280	..	.....	.....	...
6/ 7/33	....	2.4	0.110	..	.....	.....	...
6/ 8/33	19.4	...	0.330	..	.....	.....	...
6/ 9/33	15.0	2.4	0.670	..	.....	.....	...
6/13/33	14.2	2.4	0.150	..	.....	.....	...
6/14/33	14.0	...	0.220	..	.....	.....	...
6/15/33	14.5	2.6	0.600	..	.....	.....	...
6/19/33	....	...	0.310	..	.....	.....	...
6/20/33	14.8	2.3	0.540	..	.....	.....	...
6/22/33	....	...	0.400	..	.....	.....	...
6/23/33	....	...	0.660	..	.....	.....	...
6/24/33	....	...	0.360	..	.....	.....	...
6/25/33	....	...	0.680	..	.....	.....	...
6/26/33	16.8	2.0	0.740	..	.....	.....	...
6/28/33	14.5	2.2	0.140	..	.....	.....	...
6/29/33	....	...	0.350	..	.....	.....	...
6/30/33	....	...	0.370	..	.....	.....	...
7/ 1/33	....	...	0.640	..	.....	.....	...
7/24/33	8.2	...	.....	38	2,180,000	8,950	...
7/25/33	....	...	0.028	..	.....	.....	...
7/26/33	8.8	2.2	0.090	..	.....	.....	...
7/27/33	8.1	2.1	.....	38	2,400,000	7,700	...
7/28/33	6.0	...	.....	..	.....	.....	...
7/29/33	6.7	2.3	.....	..	.....	.....	...
7/31/33	6.0	...	.....	..	.....	.....	...
8/ 1/33	7.0	2.6	.....	..	.....	.....	...
8/ 2/33	7.0	2.7	.....	..	.....	.....	...
8/ 3/33	7.2	...	.....	..	.....	.....	...
8/ 4/33	7.4	...	.....	..	.....	.....	...
8/ 5/33	7.5	2.8	.....	..	.....	.....	...
9/ 7/33	7.5	2.8	.....	..	.....	.....	...
8/ 8/33	7.0	...	.....	..	.....	.....	...
8/11/33	7.5	2.7	.....	30	2,430,000	7,600	...
8/14/33	8.2	...	0.020	34	2,800,000	7,500	...
9/15/33	8.3	2.8	0.016	36	2,980,000	7,000	...
8/17/33	8.2	...	0.014	..	.....	.....	...
8/18/33	8.1	...	0.081	..	.....	.....	...
8/21/33	8.0	...	0.080	42	2,940,000	5,650	...
8/25/33	8.5	...	.....	52	3,130,000	7,100	...
9/ 6/33	8.9	...	0.020	54	3,320,000	7,900	...
9/19/33	8.2	3.2	.....	54	3,550,000	.....	...
10/ 5/33	10.0	...	.....	54	3,370,000	9,850	...
10/16/33	10.0	3.4	.....	58	3,780,000	10,400	25
10/25/33	9.6	...	.....	64	3,800,000	6,600	...
11/ 1/33	10.2	...	.....	68	3,860,000	9,650	37
11/15/33	9.6	...	.....	72	4,100,000	12,500	...
12/ 2/33	9.4	...	.....	80	4,450,000	12,600	...
5/22/34	...	...	.....	83	4,580,000	7,900	...

The most pertinent laboratory findings are summarized in table 1. Before operation the calcium content of the blood was persistently high. Immediately after operation there was a sharp drop in the calcium content to a point well below normal. Subsequently the calcium content gradually assumed a normal level. These findings will be discussed later. The phosphorus content of the blood (table 1) was within normal limits. After operation the readings were

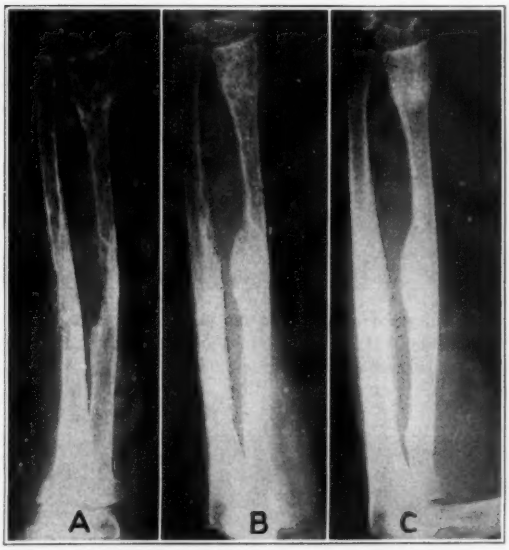

Fig. 1.—*A*, the left radius and ulna, showing marked osteitis fibrosa cystica (May 23); *B*, seven weeks postoperatively, showing marked recalcification; *C*, five months later, showing complete restoration of the bone.

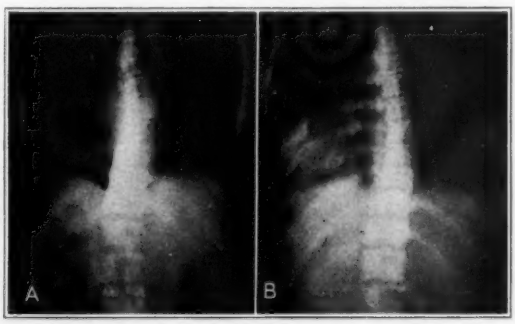

Fig. 2.—*A*, a roentgenogram showing cystic areas in the ribs (May 23); *B*, four months later, showing marked recalcification.

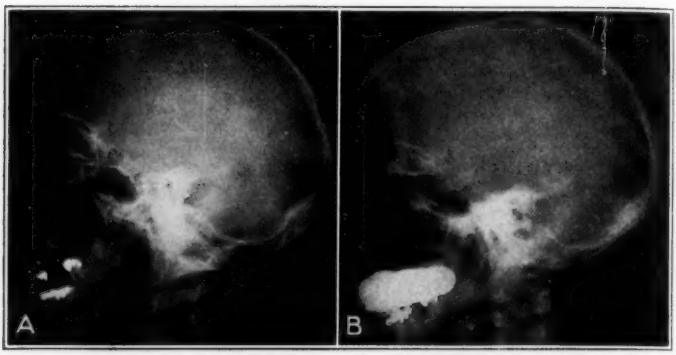

Fig. 3.—*A*, a roentgenogram showing the punched-out areas of the skull, with thickening of the tables (May 23); *B*, five months later, showing recalcification and restoration of tables of the skull.

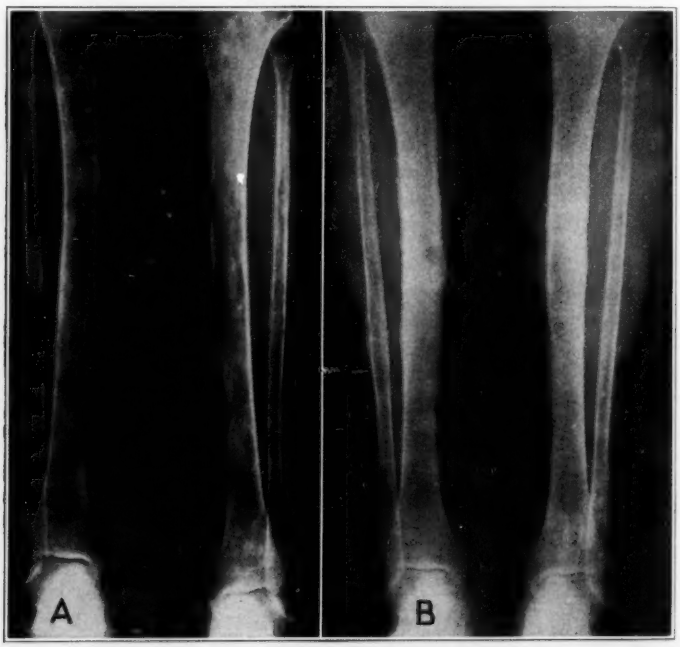

Fig. 4.—*A*, typical osteitis fibrosa cystica of both femurs and tibias (May 23); *B*, five months later.

somewhat higher, however. Numerous determinations of the amount of calcium excreted in the urine were made while the patient was taking a diet containing 0.5 Gm. of calcium a day, and the results are shown in the same table. The hemoglobin value and the erythrocyte count also are recorded in table 1. The phenolsulfonphthalein elimination was 18 per cent in the first hour, 8 per cent in the second hour and 12 per cent in the third hour. Bence-Jones' protein was not found in the urine. The urine occasionally showed a trace of albumin, and the specific gravity in specimens examined as a routine showed a tendency to be fixed at a low level, the readings ranging between 1.004 and 1.010.

While the patient was being observed in the hospital she was comfortable, but she complained of increasing muscular weakness. The weight decreased to 99 pounds (50 Kg.). The pulse rate was rapid, ranging from 90 to 120 per minute. Because of the persistently rapid pulse rate, a determination of basal metabolism was made on June 23. The reading was + 38 per cent. This test was repeated on three successive days, and the readings were + 43 per cent, + 38 per cent and + 30 per cent, respectively. The patient was given 10 drops of compound solution of iodine three times a day, and on July 11 the basal metabolic rate was + 11 per cent. The increased metabolic rate, the rapid pulse, the hyperactive reflexes and the loss of weight, together with the therapeutic response to compound solution of iodine, indicated the presence of complicating hyperthyroidism. During the period of observation between May 19 and July 11 rapidly progressive decalcification, as indicated by roentgenograms, was observed.

Operation.—Dr. A. R. Colvin was called in surgical consultation at that time, and an operation was performed on July 21. A thorough exploration for parathyroid tissue was carried out without success. In view of the clinical picture of hyperthyroidism, it was deemed advisable to perform a subtotal thyroidectomy. It was hoped that at the same time some parathyroid tissue might be removed. The entire left lobe of the thyroid gland, together with the posterior capsule, was therefore resected, and a portion of the right lobe, including a small adenoma, also was excised. Further exploration of the base of the neck and the superior portion of the mediastinum revealed a cystic mass, about 4 by 2 cm. in diameter, behind the manubrium of the sternum. This cyst was ruptured during removal, and brownish fluid escaped. The solid portion of the tumor was yellowish brown, and its gross appearance was suggestive of parathyroid tissue. This impression was confirmed by microscopic section.

Pathologic Report.—The tissue received in the laboratory consisted of several pieces of thyroid gland weighing 28 Gm. One piece appeared to be a complete lobe of the thyroid gland. On incision this tissue showed a uniform glossy surface the appearance of which did not suggest hyperplasia. There were no adenomatous nodules present here and nothing recognizable as parathyroid tissue. A second irregular piece of thyroid tissue of similar appearance, apparently representing a portion of a lobe, also was present. The specimen included a third piece of tissue, which proved to be a well defined thyroid adenoma about 2 cm. in diameter. On section the surface of this nodule showed the presence of colloid, but no evidence of hyperplasia was seen. The fourth piece of tissue appeared to be a collapsed cyst, the diameter of which when distended was estimated to have been 4 by 2 cm. The cyst was unilocular, and most of its wall was thin, fibrous and translucent. Forming one wall of the cyst was a mass of fleshy tissue measuring about 3 by 2 cm. On section the surface of this tissue was found to be yellowish brown, homogeneous and friable. The tumor proved to be a cystic parathyroid adenoma.

Microscopic sections of the parathyroid tissue (fig. 5), stained with hematoxylin and eosin, showed it to be composed for the most part of clear (*wasserhelle*) cells arranged in sheets and supported by a fine reticulum of connective tissue. These cells were polyhedral and showed well demarcated membranes, giving large areas of the tumor a mosaic appearance. The cytoplasm of these cells was clear or slightly foamy, and the nuclei were round and vesicular, showing prominent nucleoli. There were some large pyknotic nuclei and occasionally a multinucleated cell. Numerous irregular mitoses were seen in these cells. Only a few oxyphilic cells were seen, usually occurring singly or in small groups. They were somewhat larger than the clear cells and more irregular in outline. The cytoplasm was pink staining and granular, and the nuclei were somewhat larger than those of the clear cells. The chromatin of the nuclei was more compact; no nucleoli were seen. Cells of a third type occurred in dense clumps or occasionally

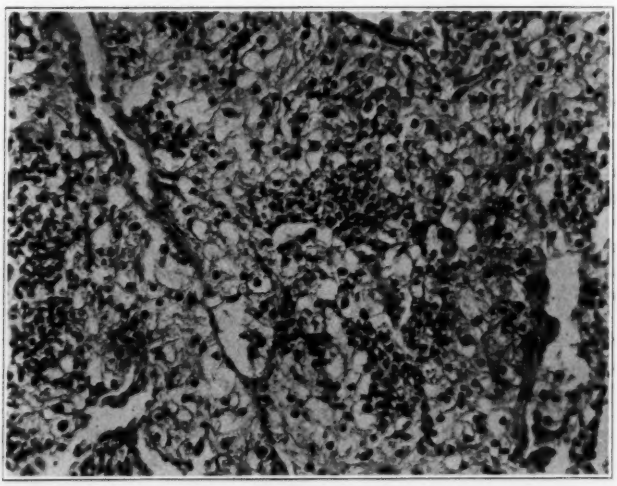

Fig. 5.—Microscopic section of the parathyroid adenoma.

formed regular columns or strands. The cytoplasm of these cells was not prominent, but each nucleus was small, dense and deep staining and was situated at the base of the cell. This undoubtedly was the principal type of cell. Transitions between this cell and the well formed *wasserhelle* cell were present at certain points. There was no evidence of invasion of the capsule of the adenoma by any of the three types of cell, and while the tumor appeared to be rapidly proliferating, there was no evidence of malignancy.

Microscopic sections of the thyroid gland showed that the acini varied considerably in size. They all contained colloid material which had a normal staining reaction. The height of the epithelium lining these acini was practically normal, and no evidence of hyperplasia was seen. In the stroma of the gland, however, definite collections of lymphocytes were seen. The presence of the lymphocytes was the only residual histologic evidence of the hyperplasia of the thyroid gland, which must have been present before treatment with iodine was instituted.

The predominant cell in the parathyroid tissue, as shown in figure 5, was the *wasserhelle* cell. According to the classification of Castleman and Mallory,[4] the parathyroid lesion belonged to the neoplastic group. The diagnosis, therefore, was clear cell cystic adenoma of the parathyroid gland.

Course.—The patient withstood the operation well, but on the fourth postoperative day, July 25, marked muscular hyperirritability was noted, and a positive Trousseau sign developed. The calcium content of the blood on July 24 dropped to 8.2 and later (July 28) to 6 mg. per hundred cubic centimeters. Large doses of calcium and parathyroid extract were given, and the symptoms of tetany were promptly controlled. The dose of parathyroid extract was gradually decreased, and the medication was discontinued after ten days, with no recurrence of the symptoms. During this period increasing pallor was noted, and on August 8 the hemoglobin reading was 30 per cent. The anemia was treated with large doses of iron and ammonium citrates, with no improvement until intramuscular injections of liver extract were given. These were continued during the remainder of the patient's stay in the hospital, with the resulting improvement shown in table 1. In addition, calcium lactate, viosterol and heliotherapy (quartz mercury vapor lamp) were used, and a gradual improvement was noted in the patient's general condition. The pulse rate decreased, the appetite improved and there was a gain in weight.

On July 25, four days after the operation, the calcium content of the urine showed the first drop to a point below normal. This low content persisted until September 6, after which no further determinations were made. The studies of the calcium content of the blood showed a gradual increase from the low reading of 6 mg. per hundred cubic centimeters on July 28 to a normal figure. The first normal figure was not obtained, however, until October 11. The patient was discharged from the hospital on August 21. She continued to take calcium lactate, viosterol and iron and ammonium citrates, the taking of liver extract being discontinued.

After leaving the hospital the patient continued to gain rapidly in weight and strength. In September and October, however, the hemoglobin value became stationary at 54 per cent. Liver extract was again given, and (table 1) there was a rapid rise in the hemoglobin value to 80 per cent. On November 1 the basal metabolic rate was normal. The phosphorus content of the blood, which had never been low, showed a gradual rise. The last reading (September 6) was 3.4 mg. per hundred cubic centimeters of blood. Three months after leaving the hospital the patient had gained 40 pounds (18 Kg.) in weight and had returned to work, feeling better than she had in years.

Roentgenograms of the left forearm were taken at short intervals to follow the process of recalcification. These films showed beginning deposition of calcium as early as sixteen days after the operation. The first and most rapid deposition occurred in the large cystic area of the radius, which had been almost completely decalcified. Later, there was a remarkable restoration not only of the calcium content of the involved bones but also of their architecture. These changes proceeded rapidly until December 21, when the bones presented a normal appearance, save for a densely calcified cystic area and a well calcified callus in the region of the fracture. Recalcification of the balance of the skeleton showed corresponding improvement. The accompanying illustrations (figs. 1 to 4) show the conditions at that time. Roentgenograms taken in March 1935 showed even greater improvement.

4. Castleman, B., and Mallory, T. B.: Am. J. Path. **11**:1, 1935.

TABLE 2.—*Summary of the Cases Reported in the Literature*

Authors	Year	Age of Patient, Years	Sex	Type of Parathyroid Tissue Removed	Duration of Symptoms Before Diagnosis	Basal Metabolic Rate	Length of Time Patient Was Followed	Degree of Recalcification of Bone	Clinical Result
Boyd, J. D., and Milgram, J. E.: J. A. M. A. **93**: 684, 1929	1929	21	M	Normal and cystic degeneration	3-5 yr.	....	2 mo.	None	Improved
Barr, D. P.; Bulger, H. A., and Dixon, H. H.: J. A. M. A. **92**: 951 1929	1929	56	F	Adenoma	8 yr.	....	.....	.....	Improved
Wilder [10]	1929	32	F	Adenoma	6 yr.	+12, +2	4 mo.	Moderate	Improved
Snapper, I.: Arch. Int. Med. **46**: 506, 1930	1930	56	M	Adenoma	7 yr.	....	9 mo.	.....	Improved
McClellan and Hannon [11a].....	1930	30	M	.....	8 yr.	—8, —17	13 yr.	None	Died
Ballin and Morse [11c].....	1931	50	..	Tumor	10 yr.	....	.....	.....	Died
	1931	17	M	Parathyroid hyperplasia	.....	....	.....	.....	Died
	1931	65	M	.....	3 yr.?	....	4 mo.	Moderate	Improved
	1931	..	M	3 parathyroid glands	1 yr.	....	5 mo.	.....	Improved
	1931	63	F	2 parathyroid glands, with cystic degeneration	.....	+25	.....	.....	Improved
Schnabel, T. G.: M. Clin. North America **14**: 977, 1931	1930	26	M	Adenoma	5 yr.	....	1 mo.	.....	Improved
Tavenner, J. L.: Minnesota Med. **16**: 269, 1933	1933	53	F	No operation	8 yr.	....	.....	.....	Unimproved
Struthers, J. W.: Edinburgh M. J. **40**: 37, 1933	1933	47	M	Adenoma	5 yr.	....	.....	.....	Died
	1933	38	F	Parathyroid hyperplasia	10 yr.	....	?	.....	Died
	1933	48	F	Adenoma	? yr.	....	.....	.....	Died
Rankin, F. W., and Priestley, J. W.: Am. J. Surg. **20**: 298, 1933	1933	34	F	Thyroid adenoma; lobectomy	3+ yr.	+12, +21	4 mo.	Slight	Improved
	1933	47	F	Adenoma	4 yr.	....	3 mo.	None	Died
Elmslie, R. C., and others: Brit. J. Surg. **20**: 479, 1933	1933	42	F	Tumor	10 yr.	....	2 yr.	None in 6 mo.; definite in 2 yr.	Improved
	1933	26	F	Tumor	2 yr.	....	9 mo.	Definite	Improved
	1933	23	F	Tumor	8 yr.	—22	16 mo.	None in 5 mo.; definite in 16 mo.	Improved
Cohen, H., and Kelly, R. E.: Brit. J. Surg. **20**: 472, 1933	1933	48	F	Tumor (principal cell)	9 yr.	....	3 mo.	Moderate	Improved
Rosedale, R. S.: Am. J. Path. **8**: 745, 1932	1932	50	F	Tumor	7 yr.	....	4 days	.....	Died
Hitzrot, L. H., and Comroe, E. L.: Arch. Int. Med. **50**: 317, 1932	1932	42	F	3 normal parathyroids; thyroidectomy	4 yr.	+11	5 mo.	None in 3 wk.; improved in 9 wk.	Improved
Compere, E. L.: Surg., Gynec. & Obst. **50**: 783, 1930	1930	59	F	Adenoma	5 yr.	....	5 mo.	None	Improved
Gold, E.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **61**: 63, 1928	1928	54	F	Adenoma	.....	....	1 mo.	.....	Improved
Barr, D. P., and Bulger, H. A.: Am. J. M. Sc. **170**: 449, 1930	1930	38	M	Parathyroid hyperplasia	2 yr.	....	2 mo.	.....	Improved
	1930	46	F	Parathyroid hyperplasia	2 yr.	....	.....	None	Died; no operation
	1930	59	M	None found	7 yr.	+17, +27, +27, decline	.....	None	Unimproved

Ball [12]	1930	50	M	None found	7 yr.	+17, +27, +1⅞ (iodine therapy)	.....	None	Unimproved
Pemberton, J., and Geddie, K. B.: Am. J. Surg. **92**: 202, 1930	1930	14	F	Tumor	16 mo.	....	.....	None	Improved
Wendel [11a]	1930	17	M	Parathyroid hyperplasia	1 yr.	....	.....	.....	Improved
Thomason, G., and Smith, L.: West. J. Surg. **41**: 78, 1933	1933	41	F	Adenoma	18 mo.	....	3 mo.	.....	Improved
Noble, T. P.: J. Bone & Joint Surg. **14**: 181, 1932	1932	40	M	Adenoma	.....	....	3 days	None	Died
Cooley, T. B.: Tr. Am. Pediat. Soc. **43**: 20, 1931	1931	14	F	Cystic parathyroid gland	3½ yr.	+23	.....	Doubtful	Improved
Abel, A. L.; Thomson, G., and Hawksley, L. M.: Lancet **2**: 525, 1933	1933	58	F	Adenoma	1 yr.	....	1 yr.	.....	Improved
Churchill, E. D., and Cope, O.: Surg., Gynec. & Obst. **58**: 255, 1934	1934	46	F	Parathyroid tumor	2 yr.	....	2 yr.	Slight in 7 mo.; definite in 13 mo.	Improved
	1934	60	F	Parathyroid tumor	3 yr.	....	6 mo.	.....	Improved
	1934	13	F	Parathyroid tumor	4 yr.	....	13 mo.	Definite	Improved
	1934	41	F	Parathyroid tumor	5 yr.	....	1 yr.	.....	Improved
	1934	55	F	Parathyroid tumor	.....	....	.....	.....	.....
	1934	36	F	Parathyroid tumor	3 yr.	....	6 mo.	Marked	Improved
	1934	44	F	Parathyroid tumor	1 yr.	....	.....	.....	.....
	1934	33	M	Parathyroid tumor	2 yr.	....	3½ yr.	None	Improved
	1934	54	F	Parathyroid tumor	1 yr.	....	2 mo.	.....	Improved
	1934	53	F	Parathyroid tumor	13 yr.	....	3 mo.	None	Improved
Babcock, W. W.: S. Clin. North America **12**: 1387, 1932	1932	25	F	Adenoma	3 yr.	....	Few days	.....	Died
Keynes, G., and Taylor, H.: Brit. J. Surg. **21**: 20, 1933	1933	24	M	Cystic tumor	7 yr.	....	4 mo.	Definite	Improved
Chievitz, O., and Olsen, H. C.: Hospitalstid. **75**: 1, 1932	1931	25	F	Adenoma	4 yr.	....	6 mo.	Definite	Improved
Hellstrom, J.: Acta chir. Scandinav. **69**: 237, 1932	1932	42	F	Adenoma	5 yr.	....	5 wk.	Slight	Improved
	1932	44	F	Adenoma	5 yr.	+9	5 wk.	Slight	Improved
Morton, J. J.: Internat. Clin. **3**: 18, 1933	1933	20	F	Clear cell adenoma	.....	....	.....	.....	Improved
Beck, A.: Arch. f. klin. Chir. **152**: 123, 1928	1928	41	F	Tumor	9 yr.	....	.....	.....	.....
Albright, F.; Aub, J. C., and Bauer, W.: J. A. M. A. **102**: 1276, 1934	1934	46	F	Tumor	14 yr.	....	.....	Moderate	Improved
	1934	60	F	Tumor	3 ½yr.	....	.....	.....	Improved
	1934	13	F	Tumor	4 yr.	....	.....	Increased	Improved
	1934	41	F	Tumor	5 yr.	....	.....	.....	Improved
	1934	55	F	Tumor	5 yr.	....	.....	.....	.....
	1934	35	M	Tumor	15 yr.	....	.....	.....	Died
	1934	36	F	Tumor	3 yr.	....	.....	.....	Improved
	1934	44	F	Tumor	1½ yr.	....	.....	.....	Improved
	1934	33	M	Tumor	2 yr.	....	.....	.....	Improved
	1934	54	F	Tumor	39 yr.	....	.....	.....	Improved
	1934	53	F	Tumor	12-15 yr.	....	.....	.....	.....
	1934	51	F	Tumor	9 yr.	....	.....	.....	.....
	1934	22	M	Tumor	1 yr.	....	.....	.....	Improved
	1934	52	M	Tumor	1 yr.	....	.....	.....	.....
	1934	62	F	Tumor	7 yr.	....	.....	.....	.....
	1934	26	M	Tumor	1¼ yr.	....	.....	.....	.....
	1934	55	F	.....	1½ yr.	....	.....	.....	.....

TABLE 2.—*Summary of the Cases Reported in the Literature—Continued*

Authors	Year	Age of Patient, Years	Sex	Type of Parathyroid Tissue Removed	Duration of Symptoms Before Diagnosis	Basal Metabolic Rate	Length of Time Patient Was Followed	Degree of Recalcification of Bone	Clinical Result
Bergstrand, H.: Am. J. Cancer **21**: 581, 1934	1934	64	F	Adenoma	2 yr.	....	.....	.....	Died; no operation
Gutman, A. B.; Swenson, P. C., and Parsons, W. B.: J. A. M. A. **103**: 87, 1934	1934	34	M	Adenoma	2 yr.	+3	4 mo.	Definite	Improved
	1934	53	F	Adenoma	10 yr.	+22	6 wk.	Definite	Improved
	1934	35	F	Adenoma	16 yr.	....	.....	.....	Died
	1934	60	F	Adenoma	2 yr.	+5	.....	.....	Died; no operation
Godel, A.: Wien. klin. Wchnschr. **38**: 246, 1925	1925	42	F	Adenoma	.....	....	.....	.....	Died; no operation
Guy, C. C.: Surg., Gynec. & Obst. **48**: 557, 1929	1929	29	F	Adenoma (malignant)	.....	—4	.....	.....	Improved
Hand, J. R.: S. Clin. North America **13**: 1365, 1933	1933	39	M	Adenoma	.....	....	.....	.....	Died; no operation
Berner, D.: Virchows Arch. f. path. Anat. **282**: 680, 1931	1931	40	F	Adenoma	2+ yr.	....	.....	.....	Died; no operation
	1931	..	F	Tumor	2+ yr.	....	.....	.....	Died; no operation
Hanke, H.: Arch. f. klin. Chir. **172**: 366, 1932	1932	33	F	Adenoma	7 yr.	....	.....	.....	Died; no operation
	1932	49	F	Adenoma	6 yr.	....	.....	.....	Died; no operation
Mertz, A. A.: Illinois M. J. **62**: 468, 1932	1932	70	F	Adenoma	8 yr.	....	3 mo.	Definite	Improved
	1932	64	F	Adenoma	8½ yr.	....	.....	Progressive	Improved
	1932	73	F	Adenoma	20 yr.	....	8 days	.....	Improved
	1932	73	F	Adenoma	1 yr.	....	.....	.....	Improved
Mimpriss, T. W., and Butler, R. W.: Brit. J. Surg. **21**: 500, 1934	1934	14	M	Adenoma	6 mo.	....	8 mo.	Marked	Improved
Hunter, D.: Proc. Roy. Soc. Med. **23**: 27, 1929	1929	41	F	Adenoma	3 yr.	....	.....	.....	Improved
Allen, F. N.: Proc. Staff Meet., Mayo Clin. **6**: 684, 1931	1931	34	M	Tumor	2 yr.	....	.....	.....	Improved
Strandgaard, H.: Hospitalstid. **77**: 383, 1934	1934	47	F	Tumor	10 yr.	....	3 mo.	Definite	Improved
Lahey, F. H., and Haggart, G. E.: Surg., Gynec. & Obst. **60**: 1033, 1935	1935	62	F	Adenoma	5 yr.	+20	6 mo.	.....	Improved
	1935	53	F	Adenoma	5 yr.	....	15 mo.	.....	Improved
	1935	74	F	Adenoma	6 yr.	....	18 mo.	.....	Improved
	1935	44	F	Adenoma	2 yr.	+14	3½ yr.	.....	Improved
	1935	52	F	Adenoma	.....	....	8 mo.	.....	Improved
Hunter, D.: Brit. J. Surg. **19**: 203, 1931	1931	49	F	Parathyroid hyperplasia	8 yr.	....	.....	.....	Died
	1931	37	F	Tumor	5 yr.	....	10 mo.	.....	Improved
	1931	49	F	Parathyroid hyperplasia	8 yr.	....	10 mo.	.....	Improved
	1931	51	F	Tumor	4 yr.	....	5 mo.	.....	Improved

The relatively short period in which symptoms were presented prior to the diagnosis in this case led to an investigation of the duration of the clinical course in ninety-six cases reported in the literature which was available for study to the early part of 1934 (table 2). It is difficult to determine with accuracy the date of onset of a disease which appears so insidiously. However, for practical purposes, the time of appearance of the most common symptom, pain in the legs, or of bony deformity may be considered to represent the time of onset. In the forty-nine cases in which such information was available, it could be ascertained that the disease had an average duration of four and eight-tenths years from the onset until it was recognized clinically. While it may be granted that some of these cases would have been recognized earlier had the disease been better known, it is of interest that the shortest duration reported was eighteen months. In the present case the duration of symptoms was only six months. The markedly progressive decalcification demonstrated in this case during the short period of observation before operation is noteworthy. The progress was so rapid as to indicate the probable presence of an added decalcifying factor in this case.

The studies of Aub, Bauer, Heath and Ropes [5] have shown that in hyperthyroidism there is marked disturbance of the calcium metabolism, as evidenced by decalcification of bone. This picture of bone decalcification, which is sometimes so severe as to cause spontaneous fracture, has been described also by Krummer,[6] Bernard,[7] Plummer and Dunlap,[8] von Recklinghausen [9] and Hunter.[1] Aub and his colleagues [5] have shown that in hyperthyroidism there is an increase in the fecal excretion of calcium, in contradistinction to hyperparathyroidism, in which there is a marked increase in the urinary excretion of calcium and a normal or decreased fecal excretion. These investigators have demonstrated that there is a diminished excretion of calcium in myxedema, and they state the belief that hyperthyroidism directly affects osseous catabolism and is independent of any effect of the parathyroid gland on bone. The calcium content of the blood in the two diseases also differs. In hyperthyroidism the calcium content is normal, while in hyperparathyroidism it is almost always elevated, Wilder's [10] patient offering the only exception.

5. Aub, J. C.; Bauer, W.; Heath, C., and Ropes, M.: J. Clin. Investigation **7**:97, 1929.

6. Krummer, R. H.: Rev. méd. de la Suisse Rom. **37**:439, 1917; quoted by Hunter.[1]

7. Bernard, F.: München. med. Wchnschr. **74**:432, 1927.

8. Plummer, W. A., and Dunlap, H. F.: Proc. Staff Meet., Mayo Clin. **3**: 119, 1928.

9. von Recklinghausen, F., in Festschrift für Rudolf Virchow, Berlin, George Reimer, 1891; quoted by Hunter.[1]

10. Wilder, R. L.: Endocrinology **13**:231, 1929.

From a study of the ninety-six case reports it is difficult to determine the frequency of the association of hyperthyroidism and hyperparathyroidism. In only twelve instances was the basal metabolic rate mentioned. In eight of these cases the readings were normal. In three cases [11] the basal metabolic rate was increased, the readings being +22, +23 and +25 per cent, respectively, but no further mention of the significance of these findings is made. In the fourth case, reported by Ball,[12] the patient presented the clinical picture of hyperparathyroidism. An adenoma of the thyroid gland was present, and basal metabolic rates of from +15 to +27 per cent were recorded. By means of iodine therapy the rate was reduced to +1 per cent. Subtotal thyroidectomy was performed, but no parathyroid tissue was found. The symptoms referable to hyperthyroidism were improved, and the basal metabolic rate dropped to +12 per cent, but the picture of hyperparathyroidism continued unchanged. In the first case of hyperparathyroidism reported in this country, by McClellan and Hannon,[13] the basal metabolic rate was normal both before and after resection of normal parathyroid tissue. Later a parathyroid adenoma was found and resected. In the case reported here it is felt that the element of hyperthyroidism definitely influenced the rapidity of the course and that the removal of the thyroid gland as well as of the parathyroid adenoma influenced the rapidity and the degree of recovery.

In the series of case reports studied the postoperative results were for the most part inadequately given, especially with reference to the improvement of the condition of the bones. In only twenty-four of the ninety-six cases were results reported. In thirteen of these cases evidence of recalcification was noted at periods of from one month to two years. In four of the cases in which normal parathyroid tissue was removed no improvement was noted (table 2). From these figures it appears that recalcification of bone seldom occurs within several months after the removal of parathyroid tissue. In the case reported here evidence of recalcification was noted as early as the sixteenth day after operation.

As previously mentioned, the diagnosis of hyperthyroidism was suspected in this case because of the rapidity of the pulse rate, the loss of weight and the subjective symptoms of irritability in the absence of the objective signs of tremor and restlessness usually seen in a patient with a basal metabolic rate as high as that recorded here. Since calcium is known to have an inhibitive effect on many nervous symptoms,

11. (*a*) Wendel, N.: Deutsche Ztschr. f. Chir. **228**:551, 1930. (*b*) Cooley, T. B.: Tr. Am. Pediat. Soc. **43**:20, 1931. (*c*) Ballin, M., and Morse, P. F.: Am. J. Surg. **12**:403, 1931.

12. Ball, R. G.: Proc. Staff Meet., Mayo Clin. **5**:331, 1930.

13. McClellan, W. S., and Hannon, R. R.: J. Clin. Investigation **8**:249, 1930.

the absence of these signs might be explained by the fact that the high concentration of calcium in the serum had a sedative effect.

This patient, like many of those reported on in the literature, showed a severe grade of secondary anemia. In view of the extensive damage to the bone marrow, it is reasonable to suppose that the relationship was one of cause and effect. This theory was supported by the fact that the anemia improved concurrently with the repair of the bony architecture, though the process seemed to be hastened by the administration of iron and liver extract.

SUMMARY

A case of hyperparathyroidism characterized by rapid decalcification and recalcification of bone is reported. The patient has remained in good health for two years after removal of a parathyroid adenoma. The picture was complicated by hyperthyroidism the presence of which is believed to have influenced the course of the disease.

CLINICAL SIGNIFICANCE OF THE CHOLESTEROL PARTITION OF THE BLOOD PLASMA IN HEPATIC AND IN BILIARY DISEASES

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As early as 1862, Austin Flint Jr.[1] described what he considered to be "a new excretory function of the liver consisting in the removal of cholesterine from the blood and its discharge from the body in the form of stercorine." At this early date he had already attempted to differentiate by means of the level of the cholesterol in the blood the jaundice "dependent upon the obstruction of the bile in the one case and its suppression in the other." Not much could be done further, because the methods of extracting and estimating the pure cholesterol from the various body fluids were difficult and tedious.

In recent years interest in the relationship of the liver to cholesterol metabolism has been renewed. The impetus has come from the development of newer and more accurate methods for the determination of cholesterol in the blood, body fluids and tissues, especially since the work of Windaus, Bloor and others who have modified and improved the various procedures.

With this renewed interest in cholesterol there developed as a natural aftermath the desire to express the abnormal blood cholesterol findings in terms of liver function. The search for liver function tests, however, has so far met with pessimistic results. And it may well be in disease of an organ such as the liver, with its many diverse activities, embracing metabolic, excretory, detoxifying and synthesizing functions, that only partial functional disturbances will occur. In such an event, it is possible that several activities will show aberrations, while others will remain intact. The great size of the organ, the margin of safety, and the marked compensatory and regenerative powers of the liver have mitigated against the finding of a single liver function test to evaluate the functional and pathologic state of the organ. In previous publica-

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1. Flint, A., Jr.: Am. J. M. Sc. **44**:305, 1862.

tions we have avoided the term "liver function test" in evaluating the findings concerning the blood cholesterol and its ester in hepatic and biliary diseases and have merely attempted to correlate the findings with pathologic and clinical observations.

It is beyond the scope of this communication to consider all the experimental and clinical evidence that has been accumulated on the subject of the relationship of the liver to cholesterol metabolism. Excellent reviews that thoroughly cover this subject have been written by Hueck, Bürger, Thannhauser, Gardner and Gainsborough, Adler, Schönheimer, Leupold, Bloor, Van Slyke and Peters, Sobotka and others.

This paper deals with the study of the behavior of the plasma cholesterol and its ester in more than 500 cases of hepatic and biliary tract disease observed in the wards of the Mount Sinai Hospital, New York. In the group with hepatic damage, only those cases are presented in which there existed either clinical unanimity of diagnosis or verification of the diagnosis by observations at necropsy. Among the cases of obstructive and nonobstructive diseases of the biliary tract we have included only those in which the diagnosis was verified by operation and autopsy.

The colorimetric method of Bloor and Knudson [2] was employed. Repeated determinations are easily carried out on small amounts of blood, and the method provides a sufficient degree of accuracy for clinical purposes. Using this method, we consider the normal variation of cholesterol in 100 cc. of blood plasma to be between 150 and 220 mg., of which 50 to 70 per cent is in the form of cholesterol ester. Because of the physiologic variations in the hourly blood cholesterol levels shown by McEachern and Gilmour,[3] McClure and Huntsinger,[4] Gardner [5] and Bruger and Somach,[6] we have always obtained samples of blood before breakfast.

Since the previous publications by one of us (E. Z. E.)[7] we have been better able to evaluate the blood cholesterol partition in hepatic and biliary diseases and have usually found definite correlation between the findings in the blood and the clinicopathologic state of the liver.

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3. McEachern, J. M., and Gilmour, C. R.: Canad. M. A. J. **26**:30, 1932.

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6. Bruger, M., and Somach, I.: J. Biol. Chem. **97**:23, 1932.

7. Epstein, E. Z.: (*a*) Cholesterol Partition of Blood Plasma in Parenchymatous Diseases of Liver, Arch. Int. Med. **47**:82 (Jan.) 1931; (*b*) Cholesterol of Blood Plasma in Hepatic and Biliary Diseases, ibid. **50**:203 (Aug.) 1932.

OBSTRUCTIVE JAUNDICE

This group consists of 105 unselected instances of obstruction of the biliary duct system by neoplasms, calculi, strictures, glands, etc. All cases were verified either by operation or by autopsy. (A summary of the findings appears in table 1.)

In 82 cases (78 per cent) hypercholesterolemia was present—more than 300 mg. of total cholesterol in 100 cc. of blood plasma. The highest total was 1,500 mg. in 100 cc. found in case 1. Although in all the cases there was definite obstruction to the outflow of bile, there was no absolute parallelism between the degree of hyperbilirubinemia and hypercholesterolemia. In case 53, with an icterus index of 160, there was a total cholesterol of 395 mg., whereas in case 1, with an icterus index of 100, there was a total cholesterol of 1,500 mg. in 100 cc. of blood plasma.

Although no diagnostic significance is to be attached to it, the cases of obstruction of the biliary passages by carcinoma (1 to 52) showed a more marked hypercholesterolemia than the cases due to calculi, strictures, etc. (53 to 105).

The duration of jaundice before admission of the patient to the hospital varied from one day to several months, and the degree of hypercholesterolemia showed no relationship to the length of time until the symptoms of terminal cholemia or infection developed, after which a terminal lowering of the cholesterol figures usually occurred. In many cases of obstruction due to carcinoma the obstruction lasted for months without evidence of hepatic damage, superimposed infection or cholemia. In the cases of obstruction due to stones, the duration of the jaundice affected the hypercholesterolemia more frequently. It seemed as though complications were more common in the cases in which obstruction was caused by calculi.

The relief of the obstruction, either by removal of the calculi or by producing circuitous channels, such as cholecystogastrostomy, biliary fistula, etc., resulted in a lowering of the hypercholesterolemia.

In 23 instances of obstruction (22 per cent of our cases) hypercholesterolemia was not found; 8 were due to carcinomas and 15 to calculi in the biliary tract system. An explanation for the absence of hypercholesterolemia in these 23 cases cannot be given. However, in cases 15, 17, 21, 42, 74, 75, 96 and 103 there was only one determination of the blood cholesterol, and it is conceivable that the later level might have been higher. In cases 15, 98, 99 and 105 the degree of obstruction was slight, and the level of the blood cholesterol was correspondingly not high. In cases 21, 42, 86, 89, 90, 97 and 105 the patients were

TABLE 1.—*Obstructive Jaundice*

Case	Age	Sex	Duration of Jaundice Before Admission	Date	Icterus Index	Cholesterol, Mg. per 100 Cc. of Plasma: Total	Ester	Free	Comment
1	65	M	4 wks.	5/ 3/33	100	1,500	935	565	Carcinoma of papilla of Vater. Cholecystogastrostomy, 5/9/33. Necropsy
				5/15/33	75	940	625	315	
2	46	F	5 days	3/14/33	80	500	390	110	Operation: infiltrating carcinoma of cystic and common bile duct
				3/16/33	85	625	375	250	
3	38	M	3 wks.	12/26/30	65	750	470	280	Operation: carcinoma of papilla of Vater. Waxing and waning of icterus
				1/ 8/31	30	625	375	250	
				1/16/31	16	280	150	130	
				2/ 9/31	30	695	375	320	
				2/28/31	75	750	375	375	
4	60	M	2 wks.	4/14/31	60	625	415	210	Necropsy: carcinoma of gallbladder and cystic duct invading and stenosing common bile duct
5	66	F	2 mos.	7/29/33	120	530	375	155	Operation: carcinoma of papilla of Vater
				8/ 1/33	120	355	185	170	
6	43	M	3 wks.	9/18/31	60	470	240	230	Necropsy: carcinoma of head of pancreas
7	38	F	.....	5/17/32	110	290	170	120	Necropsy: carcinoma of head of pancreas
				5/18/32	90	310	185	125	
8	61	M	8 days	11/ 4/31	60	310	155	155	Operation: carcinoma of head of pancreas
9	70	M	7 wks.	6/ 6/33	120	570	375	195	Necropsy: carcinoma of ampulla of Vater with complete obstruction of common bile duct
10	64	M	4 days	10/29/31	50	415	270	145	Operation: carcinoma of head of pancreas
11	56	F	5 mos.	9/ 7/32	95	325	170	155	Operation: carcinoma of head of pancreas
12	45	M	5 wks.	3/24/33	90	500	250	250	Operation: carcinoma of head of pancreas
13	43	M	2 wks.	4/ 2/31	42	375	90	285	Operation: carcinoma of head of pancreas
				6/22/31	120	340	190	150	
14	72	F	2 days	4/11/33	110	315	210	105	Operation: carcinoma of gallbladder with complete obstruction of common bile duct
15	63	F	3 days	4/15/32	40	240	160	80	Operation: carcinoma of cystic duct with mtastases to glands of porta hepatis
16	41	M	6 wks.	6/16/32	105	240	160	80	Necropsy: carcinoma of head of pancreas. Jaundice had persisted since May 1932
				6/22/32	105	210	105	105	
			2d adm.	8/17/32	110	535	145	390	
17	54	M	3 wks.	9/11/33	65	280	130	150	Operation: carcinoma of head of pancreas
18	52	M	3 wks.	8/19/33	90	290	185	105	Cholecystogastrostomy 8/25/33; carcinoma of head of pancreas
				9/ 4/33	105	220	160	60	
				9/ 7/33	65	250	145	105	
				9/12/33	50	215	120	95	
19	70	M	1½ wks.	8/19/32	100	225	115	110	Necropsy: carcinoma of head of pancreas
20	59	M	3 wks.	3/13/31	200	415	235	180	Clinically patient went into cholemia. Necropsy 4/4/31: carcinoma of head of pancreas, stenosing common bile duct with cholangeitic abscesses of liver. Note drop of total and ester cholesterol with increasing jaundice day before death
				4/ 3/31	250	270	50	220	
21	32	F	1 mo.	3/26/30	100	225	105	120	Operation, 3/24/30: carcinoma of head of pancreas. Cholemia. Patient died 4 days after operation
22	40	F	4 wks.	11/ 5/30	80	470	270	200	Operation: carcinoma of head of pancreas
23	43	M	3 wks.	1/29/31	35	355	150	205	Operation: carcinoma of gallbladder with metastases to porta hepatis
				2/ 5/31	25	535	290	245	
				3/ 6/31	..	340	270	70	

TABLE 1.—*Obstructive Jaundice—Continued*

Case	Age	Sex	Duration of Jaundice Before Admission	Date	Icterus Index	Cholesterol, Mg. per 100 Cc. of Plasma			Comment
						Total	Ester	Free	
24	57	F	10 days	1/14/31	56	315	105	210	Operation: metastatic carcinoma of liver and of hilar lymph nodes
				1/29/31	55	340	105	235	
25	46	M	2 mos.	3/11/33	160	280	190	90	Necropsy: carcinoma of gallbladder with metastases to hilar lymph nodes
26	55	F	10 wks.	5/11/32	125	340	115	225	Necropsy: complete obstruction of common duct by calculi; scirrhous carcinoma of extrahepatic bile ducts
27	52	M	9 mos.	9/ 3/30	85	535	60	475	Necropsy: carcinoma of head of pancreas with stenosis of papilla of Vater. Jaundice for 9 months before admission. Note low ester
28	55	M	3 wks.	2/27/31	110	680	470	210	Necropsy: occlusion of papilla of Vater by carcinoma
				3/ 2/31	60	935	625	310	
				3/11/31	48	625	375	250	
				3/24/31	70	660	430	230	
29	72	M	1 wk.	6/23/31	30	310	210	100	Obstruction of common bile duct; aspiration of liver revealed adenocarcinoma cells
30	45	M	10 days	4/30/32	100	470	310	160	Operation, September 1928: adenocarcinoma of stomach. Increasing icterus before admission
				5/ 3/32	140	570	340	230	
31	65	M	10 days	8/ 9/33	130	415	200	215	Cholecystostomy 8/12/33: profuse biliary drainage. Patient drowsy, disoriented; cholemic, 8/19/33. Note low ester. Necropsy: carcinoma of head of pancreas infiltrating common bile duct
				8/19/33	35	190	45	145	
32	52	M	14 days	9/ 1/33	60	415	220	195	Cholecystogastrostomy, 9/5/33: carcinoma of head of pancreas
				9/ 5/33	80	290	95	195	
				9/ 9/33	35	170	45	125	
33	40	M	1 day	3/ 7/34	8	250	75	175	Necropsy: carcinoma of testis with diffuse metastases in liver and lymph nodes. Compression of common hepatic duct by nodes
				4/18/34	40	410	135	275	
				4/26/34	85	...	...	...	
34	40	F	3 mos.	6/ 1/34	110	340	235	105	Cholecystogastrostomy, 6/8/34: carcinoma of head of pancreas. Patient died 6/9/34
				6/ 7/34	90	400	235	165	
				6/ 9/34	..	155	45	110	
35	35	M	2 days	1/30/34	35	375	210	165	Cholecystogastrostomy, 2/13/34; carcinoma of head of pancreas
				2/19/34	18	300	145	155	
				2/23/34	14	220	80	140	
36	32	M	5 wks.	7/21/30	150	800	90	710	Necropsy: adenocarcinoma of rectum; infiltration and occlusion of common bile duct by metastatic hilar nodes. Low ester unexplained
				7/28/30	...	680	90	590	
				8/ 5/30	...	520	75	445	
				8/14/30	150	585	35	550	
37	66	F	2 wks.	5/20/30	150	750	235	515	Operation, 6/2/30: carcinoma of papilla of Vater. Drainage by tube in common bile duct for 12 days
				5/26/30	...	600	215	385	
				6/ 4/30	...	225	30	195	
38	53	M	6 wks.	11/ 2/32	220	325	210	115	Cholecystogastrostomy, 11/8/32: carcinoma of head of pancreas. Necropsy confirmed diagnosis
				11/23/32	50	270	215	55	
39	65	F	4 days	3/15/34	100	325	235	90	Operation: carcinoma of the cystic duct with obstruction of the common bile duct
				3/22/34	...	240	45	195	
40	60	M	4 wks.	2/23/34	105	1,165	750	415	Cholecystogastrostomy, 3/2/34: carcinoma of head of pancreas
				3/ 7/34	104	535	310	225	
				3/10/34	68	440	235	205	
				3/24/34	30	470	340	130	
41	71	M	.....	2/ 3/32	75	310	180	130	Operation: carcinoma of head of pancreas
42	69	F	1 day	6/17/33	44	190	40	150	Necropsy: carcinoma of gallbladder with perforation and abscess of liver; biliary peritonitis
43	42	M	2 wks.	12/27/34	80	310	260	50	Operation: carcinoma of head of pancreas
				1/ 3/35	180	310	100	210	

TABLE 1.—*Obstructive Jaundice—Continued*

Case	Age	Sex	Duration of Jaundice Before Admission	Date	Icterus Index	Cholesterol, Mg. per 100 Cc. of Plasma			Comment
						Total	Ester	Free	
44	58	F	2 wks.	10/30/34	130	450	330	120	Operation, 11/7/34: carcinoma of head of pancreas. Cholecystostomy with profuse drainage
				11/ 5/34	110	415	235	180	
				11/15/34	80	440	165	275	
45	53	M	6 wks.	12/18/33	110	750	540	210	Cholecystogastrostomy, 1/3/34: carcinoma of head of pancreas
				12/22/23	90	535	310	225	
				1/17/34	35	240	65	175	
46	54	M	1 day	12/ 5/34	68	340	170	170	Operation, 12/12/34: carcinoma of common bile duct. Cholecystogastrostomy
				12/12/34	120	420	210	210	
				12/17/34	38	340	145	195	
47	36	M	10 wks.	2/17/34	120	375	125	250	Operation: scirrhous carcinoma of hepatic bile duct with obstruction
48	56	M	3 days	9/17/34	20	315	235	80	Operation, 10/12/34: carcinoma of head of pancreas
				9/28/34	40	260	120	140	
				10/ 8/34	90	270	150	120	
49	64	F	3 wks.	10/23/34	35	340	105	235	Operation, 11/21/34: carcinoma of gallbladder with obstruction of common bile duct
				10/29/34	45	325	265	60	
				11/ 3/34	80	415	265	150	
				11/16/34	77	500	375	125	
50	55	M	.....	12/14/34	50	375	195	180	Necropsy: carcinoma of stomach; metastases to porta hepatis, obstructing common bile duct
51	31	F	2 mos.	10/22/34	110	1,170	1,040	130	Operation: carcinoma of stomach with metastases obstructing common bile duct
52	58	F	7 days	1/ 8/34	110	470	245	225	Operation, 1/12/34: adenocarcinoma of gallbladder with infiltration of common bile duct
				1/15/34	120	290	110	180	
				1/22/34	85	235	120	115	
				2/ 5/34	80	290	145	145	
53	52	F	5 wks.	2/13/31	160	395	210	185	Operation: stones in common bile duct and gallbladder
54	58	F	2 wks.	11/ 6/32	90	360	200	160	Operation: stones in common bile duct
55	52	M	6 days	12/ 1/32	70	310	155	155	Operation: stone in common bile duct
56	41	F	9 days	4/10/31	45	625	470	155	Operation: large stone completely occluding common bile duct
57	52	F	"few days"	5/ 3/33	105	340	210	130	Operation: common bile duct distended with stones
58	48	F	.....	6/ 6/33	11	440	255	185	Operation: common bile duct markedly dilated with large and small stones. Note: Hypercholesterolemia preceded icterus
				6/ 8/33	33				
59	69	F	12 wks.	7/12/33	95	325	180	145	Operation: common bile duct dilated with stones
60	65	M	8 days	2/24/33	80	330	250	80	Operation: stone in common bile duct
61	57	F	5 wks.	3/ 7/33	25	340	165	175	Operation: one large and several smaller stones in common bile duct
62	65	F	1 mo.	11/30/31	30	310	170	140	Operation: common bile duct markedly distended with stones
63	61	M	3 days	4/27/33	35	300	160	140	Operation: large stone in common bile duct
64	44	F	2 mos.	3/29/33	50	375	265	110	Operation, 4/3/33: stones in common bile duct
				4/ 7/33	50	290	150	140	
				4/17/33	30	290	170	120	
65	70	F	Intermittent 9 mos.	10/20/33	44	315	190	125	Operation, 10/28/33: common duct dilated and full of stones. Pathologic cholecystogastrostomy found. Drain in common bile duct until 11/29/33
				11/ 1/33	20	250	100	150	
66	39	M	1 day	2/12/33	35	340	155	185	Operation: common bile duct dilated with stones
67	28	M	6 days	4/23/31	140	375	170	205	Operation: common bile duct obstruction by echinococcus cyst
68	38	F	.....	3/17/31	75	270	150	120	Operation: common bile duct obstructed by traumatic stricture
				3/24/31	65	360	200	160	
				3/28/31	80	380	150	230	

TABLE 1.—*Obstructive Jaundice—Continued*

Case	Age	Sex	Duration of Jaundice Before Admission	Date	Icterus Index	Cholesterol, Mg. per 100 Cc. of Plasma			Comment
						Total	Ester	Free	
69	56	F	4 wks.	1/27/33	80	340	200	140	Operation: common bile duct dilated by one large and several small stones
70	36	F	1 day	7/22/29	60	365	220	145	Operation: stones in common and hepatic bile ducts
71	62	F	3 days	11/11/30	40	585	345	240	Operation: very large stone obstructing common bile duct
72	60	M	1 wk.	11/10/30	50	535	290	245	Operation: stone obstructing common bile duct
73	59	M	10 wks	1/20/31	45	310	205	105	Operation, 1/29/31: large stone in common duct. Patient went into cholemia. Necropsy, 2/9/31
				2/ 5/31	100	215	80	135	
74	58	F	2 mos.	2/ 3/33	30	290	115	175	Operation: enormously distended common bile duct filled with calculi and masses of sand
75	29	F	2 days	12/ 3/32	80	190	100	90	Operation: stone in retroduodenal portion of common bile duct
76	44	F	2 days	4/30/30	60	250	25	225	Operation, 5/10/30: stone in common bile duct; drainage of common bile duct
				5/26/30	50	245	85	160	
				6/ 6/30	...	170	45	125	
77	42	M	4 wks.	5/22/31	105	340	210	130	Operation, 5/25/31: many stones in common bile duct. Free drainage of bile
				6/ 8/31	60	310	110	200	
				6/15/31	30	300	85	215	
78	60	M	3 wks.	7/ 1/30	50	220	80	140	Operation: large stone in common bile duct
				8/ 4/30	...	270	135	135	
79	54	M	2 wks.	5/21/34	55	340	205	135	Operation: obstruction of common bile duct by adhesions due to previous operation
				5/31/34	80	270	105	165	
				6/12/34	55	325	140	185	
80	55	M	3 days	3/26/34	50	250	75	175	Operation: common bile duct dilated with stones. Drain in common bile duct from 3/27/34-4/2/34. History of repeated attacks of jaundice in past 2 years
				3/29/34	65	215	35	180	
				4/ 4/34	40	210	65	145	
				4/28/34	13	230	115	115	
81	50	F	5 yrs.	4/16/34	45	560	290	270	Necropsy: complete stenosis of common bile duct (traumatic at operation 5 years previously); chronic cholangeitis and pericholangeitis
82	58	M	1 mo.	1/17/34 (1st adm.)	55	375	145	230	Operation, 5/19/34: markedly distended gallbladder; on aspiration foul, infected bile obtained; stones in common bile duct; cholangeitis. Profuse biliary drainage instituted. Patient entered hospital 3d time with biliary fistula from previous operation. Injection of iodized poppy-seed oil 40 per cent through drainage tube reveals markedly dilated common duct, narrowed at papilla of Vater
			2 days	5/ 9/34 (2d adm.)	35	250	50	200	
				5/24/34	27	250	Traces	+250	
				6/ 2/34	18	235	100	135	
			3 mos.	8/ 6/34 (3d adm.)	18	325	250	75	
83	26	F	8 mos.	4/21/34	83	415	170	245	Operation, 5/1/34: stricture of common bile duct (due to previous severing 7 months ago following cholecystectomy). Hepatoduodenostomy over a tube performed
			Intermittent	5/ 2/34	85	395	100	295	
				5/ 7/34	28	290	95	195	
84	29	F	3 mos.	6/ 5/34	85	415	210	205	Operation, 6/15/34: common bile duct dilated by stones
				6/12/34	...	355	145	210	
85	54	M	10 mos.	5/ 4/31	80	410	180	230	Necropsy, 11/5/31: common bile duct dilated; chronic cholangeitis with biliary cirrhosis
				10/31/31 (2d adm.)	100	270	120	150	
86	58	M	7 wks.	12/26/31	40	290	105	185	Necropsy: stone in common bile duct, occluding papilla of Vater; obstructive biliary cirrhosis
				1/ 9/31	...	155	80	75	
				1/16/31	105	130	90	40	

TABLE 1.—*Obstructive Jaundice—Continued*

Case	Age	Sex	Duration of Jaundice Before Admission	Date	Icterus Index	Cholesterol, Mg. per 100 Cc. of Plasma			Comment
						Total	Ester	Free	
87	50	F	1 yr.	1/11/32	25	470	310	160	Operation, 2/13/32: common bile duct completely severed (result of previous operation). Tube placed in proximal end of common duct and bile drained to outside
				3/ 1/32	...	260	120	140	
				3/14/32	18	190	115	75	
88	40	M	7 wks.	4/21/34	40	275	130	145	Operation: stones in gallbladder and common bile duct
				4/25/34	30	500	125	375	
				5/ 2/34	35	415	155	260	
89	62	M	.....	4/31/32	120	115	Trace	±115	Necropsy: stone in common duct with partial obstruction at ampulla of Vater; acute purulent cholangeitis, and cholangiolitis. Histologic diagnosis: degeneration of liver cells
90	50	F	1 day	10/11/32	30	190	40	150	Necropsy: stones in common mon bile duct; acute cholecdochitis; suppurative cholangeitis; abscesses of liver
91	30	F	3 wks.	1/13/35	135	310	235	75	Operation, 1/15/35: stones in common bile duct. Drained for 16 days
				1/18/35	160	235	80	155	
				1/21/35	110	210	115	95	
				1/24/35	100	150	70	80	
92	38	M	7 wks.	2/14/32	120	430	265	165	Operation, 3/7/34: stones in common bile duct
				2/22/32	80	470	310	160	
				12/18/33 (2d adm.) (3d adm.)	15	375	250	125	
				2/26/34	10	355	170	185	
93	38	M	10 days	9/21/33	30	455	250	205	Operation, 10/14/33: common bile duct and hepatic ducts enormously dilated with stones
				10/13/33	30	375	205	170	
94	50	M	9 days	8/ 9/34	26	395	170	225	Operation, 11/2/34: stones in common bile duct
				8/16/34	11	340	210	130	
				11/ 2/34 (2d adm.)	25	310	135	175	
95	60	F	3 days	5/15/34	14	480	275	205	Operation: stones in common bile duct
				5/22/34	10	340	200	140	
96	65	F	.....	11/26/32	45	280	180	100	Operation: common bile duct dilated by stones
97	35	F	1 wk.	1/17/34	42	270	95	175	Operation, 1/24/34: stone in common bile duct. Necropsy acute cholangeitis; subhepatic abscess
				1/26/34	50	250	30	220	
98	40	F	2 mos.	2/15/34	12	190	35	155	Operation, 2/27/34: stone in common bile duct. Drainage profuse
				2/19/34	22	210	70	140	
				4/ 7/34	4	155	30	125	
99	39	F	.....	4/17/34	28	265	100	165	Operation, 4/20/34: stones in common bile duct; biliary fistula for 5 weeks
				4/19/34	15	235	70	165	
				4/25/34	14	110	Trace	±110	
				5/26/34	9	170	30	140	
100	54	F	2 wks.	5/19/34	45	1,340	850	490	Operation, 5/25/34: stone occluding common bile duct
				5/26/34	60	1,070	625	445	
101	40	M	4 mos.	2/19/34	48	300	145	155	Operation, 3/6/34: common bile duct dilated with stones
				3/16/34	40	290	200	90	Reentered for persistent biliary drainage, icterus and fever. Cholangeitis
				4/12/34 (2d adm.)	60	220	65	155	
				4/23/34	50	265	100	165	
				5/14/34	40	310	135	175	
102	50	F	.....	2/27/34	20	485	300	185	Operation: stone in common bile duct
103	41	F	1 day	2/ 1/35	20	200	55	145	Operation, 2/1/35: stones in common bile duct
104	47	F	4 wks.	10/23/34	100	290	200	90	Operation, 10/29/34: stones in common bile duct. Drainage
				10/26/34	...	290	185	105	
				11/ 2/34	30	175	95	80	
105	54	F	.....	1/18/35	15	275	145	130	Operations, 1/22/35: stones in common bile duct. Necropsy, 2/4/35: acute cholangeitis
				2/ 2/35	17	200	105	95	

observed only after the occurrence of complications such as cholemia, perforation of the gallbladder with abscess of the liver, acute purulent cholangeitis and cholangiolitis (a term used to denote infections in the very fine biliary channels) with liver cell degeneration and acute choledochitis.

The cholesterol ester of the blood plasma was elevated above 150 mg. in 100 cc. in 79 of the 105 cases of obstructive jaundice (75 per cent).

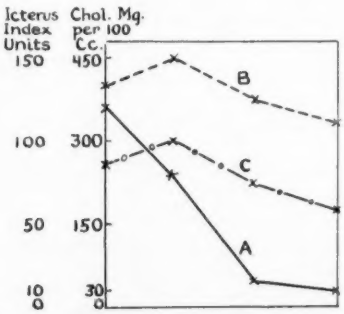

Chart 1.—A typical case of obstruction of the common bile duct by stones, with hyperbilirubinemia paralleling hypercholesterolemia (total [*B*] and ester [*C*]). With relief of the obstruction and fall of the icterus index (*A*) there was gradual lowering of the cholesterol level. Note the more rapid fall of the icterus index.

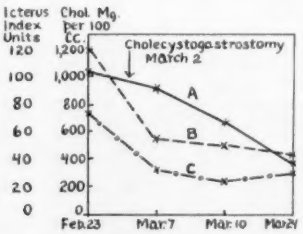

Chart 2.—A typical case of jaundice due to obstruction of the common bile duct by carcinoma of the head of the pancreas. At the onset there was the usual hyperbilirubinemia with hypercholesterolemia (total [*B*] and ester [*C*]). With relief of the obstruction by cholecystogastrostomy there was gradual lessening of the jaundice together with lowering of the cholesterol level. *A* is the icterus index.

In 7 of these 79 instances (cases 37, 61, 66, 67, 83, 85 and 94) the elevation of cholesterol ester was not proportional to the increase in the free cholesterol. With subsidence of the obstruction and lowering of the bilirubin and total cholesterol of the blood, the cholesterol ester fell proportionately.

Of the 26 instances of obstructive jaundice in which the blood cholesterol ester was below 150 mg. in 100 cc., the ester remained normal or slightly raised in 18. No explanation can be given for this failure of the cholesterol ester to rise with obstruction of the biliary tract system. In 8 cases the cholesterol ester dropped below normal. A perusal of the records on these 8 cases revealed that complications were present in 5, which would suggest secondary hepatic damage. In case 27, at the time of admission, jaundice has been present for nine

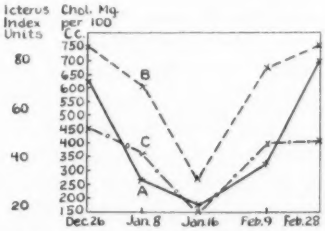

Chart 3.—A case of jaundice due to obstruction of the common bile duct by carcinoma of the papilla of Vater. Note the parallelism between the hyperbilirubinemia and the hypercholesterolemia. As the icterus index (*A*) diminished, the cholesterol (total [*B*] and ester [*C*]) also diminished, and as the jaundice increased again, the cholesterol level rose sharply. Waxing and waning of icterus were followed closely by the level of cholesterol.

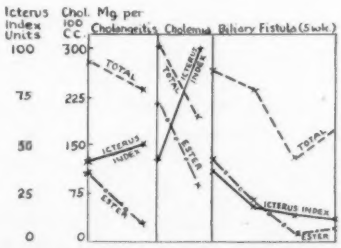

Chart 4.—Three cases of obstructive jaundice complicated, respectively, by cholangeitis, cholemia and biliary fistula. When cholangeitis and cholemia complicated the picture, the total and cholesterol ester diminished as the icterus index rose (owing to the complication of hepatic damage). In the case in which there was a biliary fistula, as the icterus index diminished, the total cholesterol fell, but the cholesterol ester was considerably lowered.

months; in case 42 there was a perforation of the gallbladder with hepatic abscesses; in case 82, at the time of entrance, the cholesterol ester was high; it dropped with the appearance of cholangeitis and returned to the former level after drainage of the common bile duct; in case 89 microscopic examination at autopsy revealed acute purulent

cholangeitis and cholangiolitis as well as liver cell degeneration; in case 90 there were suppurative cholangeitis and hepatic abscesses. In cases 76, 98 and 103 the drop in cholesterol ester was unexplainable.

COMMENT

The association of hypercholesterolemia and hyperbilirubinemia in obstructive jaundice has been emphasized in the past by many authors: Chauffard, Laroche and Grigaut,[8] Beumer and Bürger,[9] Feigl,[10] Bang,[11] Rothschild and Felsen,[12] Stepp,[13] Adler and Lemmel,[14] Gardner and Gainsborough,[15] Epstein,[7] Stroebe,[16] Mjassnikow,[17] Heinlein,[18] and Lehnherr.[19] Exceptions were noted by Stepp when such factors as cachexia and poor resorption of fat supervened over a long time, and by Rothschild and Felsen when high temperatures and infections occurred. Later, Adler, Epstein, Stroebe and others also found that infections in the biliary tract, cholemia, cachexia and damage to the liver subsequent to long-standing stasis were marked by absence of the customary hypercholesterolemia or else by a drop in an existing hypercholesterolemia in a previously uncomplicated case. Cases of obstruction complicated by severe infections usually fail to show hypercholesterolemia.

The hypercholesterolemia occurring in obstructive jaundice had been previously considered to be a retention phenomenon. This was based on the belief that cholesterol was excreted mainly by the liver. Since the work of Sperry,[20] Salomon,[21] Schönheimer,[22] Bürger and Winterseel,[23] and Bürger and Habs [24] it is known that the main excretion of

8. Chauffard, A.; Laroche, G., and Grigaut, A.: Compt. rend. Soc. de biol. **73**:23, 1912.

9. Beumer, H., and Bürger, M.: Ztschr. f. exper. Path. u. Therap. **13**:343, 1913.

10. Feigl, J.: Biochem. Ztschr. **90**:1, 1918.

11. Bang, I.: Biochem. Ztschr. **91**:122, 1918.

12. Rothschild, M. A., and Felsen, J.: Cholesterol Content of Blood in Various Hepatic Conditions, Arch. Int. Med. **24**:520 (Nov.) 1919.

13. Stepp, W.: Beitr. z. path. Anat. u. z. allg. Path. **69**:233, 1921.

14. Adler, A., and Lemmel, H.: Deutsches Arch. f. klin. Med. **158**:173, 1928.

15. Gardner, J. A., and Gainsborough, H.: Quart. J. Med. **23**:465, 1930.

16. Stroebe, F.: Klin. Wchnschr. **11**:636, 1932.

17. Mjassnikow, A. L.: Klin. Wchnschr. **11**:1910, 1932.

18. Heinlein, H.: Klin. Wchnschr. **12**:1513, 1933.

19. Lehnherr, E. R.: New England J. Med. **211**:487, 1934.

20. Sperry, W. W.: J. Biol. Chem. **71**:351, 1927.

21. Salomon, H.: Arch. f. Verdauungskr. **36**:353, 1926; **39**:46, 1926; **41**: 257, 1927.

22. Schönheimer, R.: Ztschr. f. physiol. Chem. **192**:73, 1930.

23. Bürger, M., and Winterseel, W.: Ztschr. f. d. ges. exper. Med. **66**:459, 1929.

24. Bürger, M., and Habs, H.: Klin. Wchnschr. **6**:2221, 1927.

cholesterol occurs through the intestinal mucosa. Because of the low concentration of cholesterol in the bile, it would require a complete obstruction of long duration to produce an increase of the total cholesterol from 200 to 400 mg. in 100 cc. of blood plasma. It is known that within a few days after complete obstruction of the biliary passages the cholesterol of the blood may be doubled or trebled. In the light of these facts the cause of hypercholesterolemia in obstructive jaundice remains as yet unclear.

Bürger and Gardner and Gainsborough reported that the hypercholesterolemia associated with obstructive biliary lesions is mainly due to increase in the free cholesterol fraction and that the ester cholesterol is not proportionately raised. They believed that the relatively diminished cholesterol ester of the blood represents diminished absorption. They explained it as the result of faulty absorption of fat, the absence of bile from the intestines also resulting in a reduction in absorption of the cholesterol which exists in the intestines in the form of the ester. However, these authors observed some instances of hypercholesterolemia with high esters in spite of persistent absence of bile from the intestines and failure of the resorption of fat. Stroebe also found that the hypercholesterolemia of obstructive jaundice was mainly in the form of an increase in the free cholesterol with a relative diminution in the ester. However, von Rosztóczy [25] in experimental ligation of the common bile duct in rabbits found both the free and the ester cholesterol to be increased in the blood, and only when the liver was damaged by the stasis did a change in the total cholesterol and the relationship of ester to free cholesterol occur. Likewise, Stern and Suchantke [26] found increased free and ester cholesterol in the blood after ligation of the ductus choledochus in a dog.

Our results contradict the observations of Bürger and Gardner and Gainsborough. We have found an elevation of the cholesterol esters of the blood plasma in 75 per cent of our cases of obstruction of the common duct in which little or no bile or urobilin was present in the stool. Conversely the ester of the blood may be low when bile is present in generous amounts in the intestines. In the cases of obstruction in which prolonged drainage or a biliary fistula has been instituted and nearly all the bile diverted from the intestines, the cholesterol ester is lowered considerably in some, but remains normal or elevated in a like number. It may be seen in table 1 that the degree of free and ester hypercholesterolemia does not vary in relationship to the duration of the obstructive jaundice. This has been recently confirmed experi-

25. von Rosztóczy, E.: Ztschr. f. d. ges. exper. Med. **68**:690, 1929.

26. Stern, R., and Suchantke, G.: Arch. f. exper. Path. u. Pharmakol. **115**: 221, 1926.

mentally by Hawkins and Wright,[27] who found that in dogs with biliary fistulas the absence of bile in the intestine with faulty absorption of fat does not cause the development of hypocholesterolemia with dissociation of the ester ratio.

PARENCHYMATOUS DISEASES OF THE LIVER

In this group, 111 cases of jaundice due to diffuse parenchymatous diseases of the liver are presented (table 2). Among these cases are

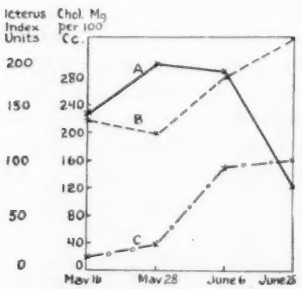

Figure 5

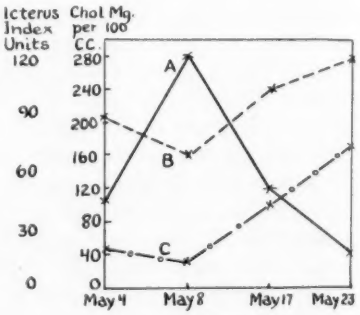

Figure 6

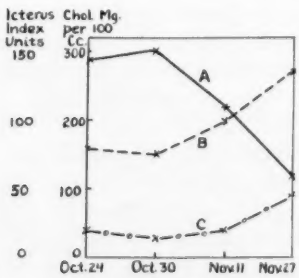

Figure 7

Charts 5, 6 and 7.—Typical cases of jaundice, occurring in the course of acute degeneration of the liver. With marked jaundice the cholesterol ester (*C*) diminished considerably, and with diminution in the icterus index (*A*) the cholesterol ester rose to normal. The ester fraction closely mirrored the severity of the damage to the liver, being low when the damage was marked and returning to normal with a favorable outcome of the case. *B* is the total cholesterol.

included instances of hepatic damage following the administration of such drugs as arsphenamine preparations, cinchophen and its derivatives, and in various diseases such as pneumonia and sepsis, and primary dis-

27. Hawkins, W. B., and Wright, A.: J. Exper. Med. **59**:427, 1934.

eases of the liver such as so-called catarrhal jaundice, toxic hepatitis and hepatosis. Acute, subacute and chronic yellow atrophy and their sequelae, the coarse nodular cirrhoses, are treated under a separate heading.

The parallelism between the bilirubinemia and cholesterolemia observed in cases of obstruction to the common bile duct was not observed in this group of parenchymatous diseases of the liver with jaundice. Although the jaundice was often intense and the icterus index reached 270 in one instance, the total blood cholesterol was above 300 mg. in 100 cc. of plasma in only 11 of 111 cases of acute degeneration of the liver as compared with 82 of 105 cases of obstructive jaundice with comparable degrees of icterus.

The divergence between the levels of the cholesterol and bilirubin in the blood in acute degeneration of the liver and the parallelism in obstructive jaundice afford valuable aid in the differentiation between the two types of jaundice.

In the remaining 100 cases of acute degeneration of the liver with considerable increase in the bilirubinemia, the total cholesterol of the blood remained below 300 mg. in 100 cc. In 24 instances the cholesterol was below 150 mg. in 100 cc. of blood plasma; in 40 instances, between 150 and 200 mg.; and in 36 instances, between 200 and 300 mg. With improvement in the clinical condition, normal cholesterol levels were reached, and during the stage of reparation and regeneration even hypercholesterolemia occurred in some cases.

In 75 cases of acute degeneration of the liver the values of cholesterol ester were found to be lowered at the onset of the illness, when the jaundice was marked and the clinical course at its height. With improvement in the condition of the patient and diminution in the jaundice, the cholesterol ester slowly rose until it reached normal and even supernormal levels. The ester fraction seems to mirror the degree of hepatic damage, tending to remain low in cases of severe hepatic injury. A persistently lowered ester level indicates an unfavorable and serious outcome, whereas a rising level parallels clinical improvement. In severe hepatic degeneration only traces of cholesterol ester may be shown during the early and most intense stage of the disease, whereas in the mild disease often only slight subnormal deviations are observed. A study of the cholesterol ester seems therefore to be of some aid in gaining an insight into both the severity of the disease and the prognosis.

From a perusal of the data on the 111 cases in table 2 it will be seen that 75 followed this simple mathematical formula of severe icterus, normal or even subnormal total cholesterol and diminished cholesterol ester. However, in 36 instances of jaundice in which the clinical picture and course were apparently similar the same results did not

occur. Here, the figures for total cholesterol and ester approached normal although the jaundice was intense and the condition of the patient appeared serious in many instances (cases 76-111 in table 2).

The explanation of the normal blood cholesterol partition in these 36 cases of acute degeneration of the liver is difficult. In the majority of these cases the disease was mild. It is possible that regeneration and reparation were sufficient to offset the damage, which was mild in spite of the intense jaundice. Klemperer,[28] in discussing the problem of so-called catarrhal jaundice, said, ". . . clinical and histological studies have shown that hepatic lesions are responsible for many of these cases. But similar considerations indicate that another group of identical symptomatology is due to ascending or descending cholangiolitis and not essentially to liver damage." The entire definition of catarrhal jaundice is rather vague, and it is possible that some of our 36 cases fall into the group mentioned by Klemperer as cases of ascending or descending cholangiolitis. Moreover, in 10 of these 36 cases of acute

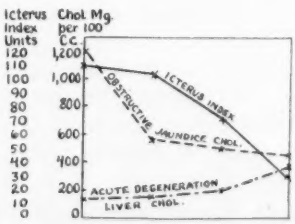

Chart 8.—The chart demonstrates the parallelism between the total cholesterol and the icterus index in obstructive jaundice and the divergence between the two in acute degeneration of the liver. This difference is of considerable aid in differentiation between the two types of jaundice.

hepatic degeneration with normal cholesterol values the condition was either associated with the secondary stage of syphilis or followed arsphenamine therapy. Bauer has likewise found that the galactose tolerance test is frequently negative in cases of jaundice in the secondary stage of syphilis or following arsphenamine therapy. Six of the 36 cases occurred in children in whom the cholesterol levels were normal.

In 4 additional cases of what appeared to be clinically acute hepatic degeneration, the total and ester cholesterol approached the high levels seen in obstructive jaundice, total cholesterol reaching 1,250 mg. in one case. No explanation could be advanced for this occurrence.[29]

28. Klemperer, P.: New York State J. Med. **33**:1309, 1933.

29. This patient suffered from marked alcoholism and after the subsidence of the jaundice had hypercholesterolemia (500 mg. in 100 cc. of plasma) for several months afterward. This case was considered to be one of toxic hepatitis complicating extreme fatty degeneration of the liver.

TABLE 2.—*Jaundice in Parenchymatous Disease of the Liver*

Case	Age	Sex	Duration of Jaundice Before Admission	Date	Icterus Index	Cholesterol, Mg. per 100 Cc. of Plasma			Comment
						Total	Ester	Free	
1	19	M	3 wks.	11/12/31	150	185	60	125	Vomiting, weakness and painless jaundice 3 weeks; enlarged liver and spleen. Patient improved rapidly
				11/17/31	95	190	135	55	
				11/27/31	75	290	155	135	
2	25	M	7 wks.	6/25/31	45	145	40	105	Jaundice 7 weeks; liver below umbilicus, tender; spleen palpable. Patient gradually improved
				6/29/31	35	200	50	150	
				7/ 6/31	40	325	80	245	
				7/20/31	30	310	135	175	
3	38	M	4 days	8/ 5/32	150	195	30	165	Headaches, weakness, chills and painless jaundice 4 days; liver enlarged slightly. Patient improved rapidly
				8/12/32	60	270	170	100	
4	19	M	4 days	12/31/31	150	105	30	75	Miliary tuberculosis of lung and skin; hepatosplenomegaly; jaundice, which gradually improved; general condition bad; patient emaciated
				1/18/32	55	220	115	105	
				2/ 5/32	20	120	30	90	
5	32	M	1 day	3/17/32	60	135	Traces	±135	Headache, malaise and joint pains 1 week; vomiting 4 days; jaundice 1 day; liver tender; spleen palpable. Patient improved
				3/22/32	90	175	110	65	
				4/ 2/32	30	270	145	125	
6	15	F	2 days	6/10/32	20	220	55	165	Nausea and malaise 6 days; jaundice 2 days; condition considered mild hepatitis
				6/18/32	13	245	135	110	
7	36	F	3 days	4/20/32	120	130	45	85	Generalized aches and pains 2 weeks; jaundice 3 days; positive galactose test. Patient improved in 3 weeks
				4/27/32	115	140	50	90	
				5/ 9/32	30	250	185	65	
8	22	M	9 days	11/16/32	160	220	40	180	Anorexia and malaise 2 weeks; jaundice 9 days; liver enlarged; spleen palpable. Patient improved rapidly
				11/22/32	50	300	135	165	
9	28	M	10 days	5/16/31	120	235	Traces	±235	Painful, swollen joints with fever for 1 month followed 10 days later by increasing jaundice; liver percussed small; condition considered at first acute yellow atrophy. Patient gradually improved: one year later perfectly well
				5/26/31	220	210	40	170	
				6/ 6/31	210	285	160	125	
				6/25/31	75	375	155	220	
10	17	M	1 day	8/10/33	17	200	55	145	Anorexia 2 days; jaundice 1 day; liver enlarged; spleen palpable, soft; mild hepatitis. Patient improving rapidly
				8/18/33	16	200	65	135	
				9/ 1/33	12	300	155	145	
11	38	M	12 days	11/ 3/33	50	200	45	155	Six weeks ago giant urticaria; nausea and diarrhea 3 weeks; jaundice 12 days; liver enlarged. Patient improved rapidly
12	14	M	5 days	3/13/33	27	200	70	130	Nausea and anorexia 1 week; jaundice 5 days; condition considered mild catarrhal jaundice. Patient improved rapidly
				3/16/33	20	220	90	130	
				3/28/33	15	260	110	150	
13	21	F	3 days	8/29/31	30	185	Traces	±185	Fever, generalized aches and pains 10 days; nausea, vomiting 8 days; jaundice 3 days; liver and spleen enlarged. Patient improved; 1 year later, well
				9/10/31	12	220	60	160	
14	34	M	6 days	5/10/32	35	165	30	135	Anorexia and nausea 2 weeks; jaundice 6 days; liver enlarged. Patient well and discharged at end of 1 week
15	43	F	1 day	7/11/31	110	195	70	125	Five days of nausea, vomiting, eruption on legs; jaundice 1 day; liver enlarged; spleen palpable; two years later, patient well
				7/22/31	105	235	50	185	
				7/27/31	60	270	140	130	
16	26	F	5 days	6/30/33	35	210	65	145	Chills and fever with painless jaundice 5 days, considered mild attack of toxic hepatitis. Patient improved rapidly

TABLE 2.—*Jaundice in Parenchymatous Disease of the Liver—Continued*

Case	Age	Sex	Duration of Jaundice Before Admission	Date	Icterus Index	Cholesterol, Mg. per 100 Cc. of Plasma: Total	Ester	Free	Comment
17	26	M	2 days	10/ 1/31	110	170	Traces	+170	Joint pains, anorexia and loss of weight 4 weeks; jaundice 2 days; liver enlarged; spleen palpable. Patient gradually improved
				10/ 5/31	45	200	65	135	
				10/ 7/31	45	185	25	160	
18	24	M	10 days	9/ 5/30	60	180	40	140	Malaise and painless jaundice 10 days; liver enlarged; acute toxic hepatitis. Patient improved; December 1930, well
19	26	M	4 days	9/11/33	110	150	Traces	+150	Headache, anorexia, jaundice 4 days; liver and spleen enlarged. Patient left hospital against advice. Catarrhal jaundice
20	22	M	9 days	3/14/33	30	140	55	85	Nausea, vomiting and painless jaundice 9 days; liver and spleen enlarged. Patient improved rapidly
				3/18/33	45	175	75	100	
21	28	F	15 days	10/24/33	140	155	35	120	Malaise, anorexia, vomiting and jaundice 15 days; patient very sick and toxic; improved slowly
				10/30/33	150	150	20	130	
				11/11/33	110	190	25	165	
				11/27/33	70	270	80	190	
22	23	M	2 days	10/30/33	80	190	50	140	Anorexia, nausea and weakness 9 days; jaundice 2 days; liver enlarged. Patient gradually improved
				11/ 1/33	50	190	90	100	
				11/ 5/33	38	240	60	180	
23	48	F	1 wk.	9/26/32	70	200	60	140	Ingestion of atophan for 1 week followed by painless jaundice 1 week later; liver enlarged; toxic hepatitis following atophan. Patient improved
24	26	M	1 day	9/10/31	95	185	Traces	+185	Headache, fever and anorexia 9 days; jaundice 1 day; liver enlarged; spleen palpable. Patient improved
				9/22/31	25	220	35	185	
25	32	M	6 days	4/ 8/30	70	150	Traces	+150	Anorexia, belching and diarrhea 10 days; jaundice 6 days; liver enlarged. Patient improved
				4/18/30	120	215	55	160	
				5/14/30	20	310	190	120	
26	52	M	36 hrs.	12/16/29	35	240	55	185	Jaundice after intravenous hypertonic saline infusions for thrombo-angiitis obliterans. Patient improved after 12 weeks
				2/10/30	12	220	170	50	
27	40	M	.....	4/ 2/30	75	120	Traces	+120	Patient entered hospital for malnutrition. After 12 doses of luminal generalized dermatitis developed, followed 13 days later by jaundice; condition considered toxic hepatitis following ingestion of luminal
				4/ 8/30	35	150	35	115	
				4/14/30	25	275	135	140	
28	31	F	10 days	5/10/30	100	140	Traces	+140	Following ingestion of large doses of cinchophen, jaundice developed; liver and spleen enlarged; condition thought at first to be atrophy of liver. Patient very ill; improved slowly
				5/17/30	100	155	65	90	
				5/26/30	100	310	170	140	
				6/ 8/30	40				
29	39	F	1 wk.	7/12/30	70	135	50	85	Progressive painless jaundice, anorexia and nausea 1 week; subacute hepatitis. Patient improved rapidly
				7/24/30	30	190	140	50	
30	24	M	2 wks.	7/30/30	200	135	Traces	+135	Nausea, vomiting, painless jaundice; liver enlarged. Patient improved gradually
				8/ 4/30	30	190	60	130	
31	41	M	1 day	12/30/30	140	100	35	65	Jaundice in the course of lobar pneumonia of entire left lung. Necropsy: degeneration of liver
32	51	M	1 day	10/20/32	40	270	90	180	Diarrhea 2 weeks; jaundice 1 day; liver enlarged and tender; subacute hepatitis. Patient improved rapidly
				10/31/32	20	200	55	145	
33	19	M	2 days	9/24/32	100	190	70	120	Diarrhea 2 weeks; anorexia and nausea 1 week; jaundice 2 days; liver slightly enlarged. Patient improved rapidly

TABLE 2.—*Jaundice in Parenchymatous Disease of the Liver—Continued*

Case	Age	Sex	Duration of Jaundice Before Admission	Date	Icterus Index	Cholesterol, Mg. per 100 Cc. of Plasma: Total	Ester	Free	Comment
34	47	M	3 days	6/21/31	100	250	100	150	Nausea and vomiting 2 weeks, following medication; jaundice 3 days; liver enlarged.
				6/29/31	55	310	60	250	
				7/ 6/31	30	250	145	105	
				7/13/21	38	355	120	235	Patient improved gradually
35	52	F	5 days	5/17/33	75	235	95	140	Headaches, nausea and anorexia 5 weeks; arthritic pains 2 weeks; jaundice 5 days; liver enlarged, slightly tender.
				5/25/33	35	235	65	170	Patient improved
36	52	M	3 days	4/24/33	240	180	100	80	Vomiting 5 days; jaundice 3 days; liver enlarged.
				5/ 1/33	120	190	75	115	
				5/10/33	120	155	35	120	Patient improved slowly
				5/15/33	125	170	75	95	
37	38	F	.....	2/14/34	22	145	50	95	Jaundice developed in the course of pneumonia of left lower lobe; liver enlarged.
				2/19/34	12	260	120	140	Patient recovered rapidly
38	29	F	.....	10/ 7/33	16	160	40	120	Jaundice developed in the course of pneumonia of left upper and left lower lobe.
				10/13/33	11	235	125	110	Patient improved rapidly
39	28	F	8 wks.	5/ 4/34	250	165	30	135	Eight weeks painless jaundice with abdominal enlargement 1 week; liver and spleen enlarged; ascites. Condition considered at first subacute yellow atrophy.
				5/ 8/34	145	175	40	135	
				5/16/34	70	270	115	155	Patient gradually improved
40	11	M	1 day	1/13/34	40	165	40	125	Jaundice 9 days after drainage of abscess of right foot. Condition considered toxic hepatitis. Patient improved
41	30	M	2 days	5/ 4/34	45	210	50	160	Anorexia, nausea, painless jaundice few days; liver percussed small.
				5/ 8/34	120	170	40	130	
				5/17/34	38	250	115	135	
				5/23/34	22	300	170	130	Patient improved gradually
42	45	M	4 wks.	3/27/34	48	190	35	155	Alcoholic sprees; anorexia and loss of weight; jaundice 4 weeks; liver enlarged.
				4/ 7/34	15	250	55	195	Patient improved
43	34	M	2 days	4/20/34	70	265	80	185	Upper respiratory infection followed by jaundice; liver and spleen enlarged; mild toxic or infectious hepatitis.
				4/28/34	40	395	235	160	Patient improved
44	40	M	.....	1/ 2/35	85	110	40	70	Pneumonia of left lower, right lower, and right middle lobe, followed by jaundice.
				1/ 9/35	20	200	70	130	
				1/22/35	12	190	45	145	Patient improved gradually
45	45	M	1 wk.	10/ 9/34	150	135	55	80	Following alcoholic spree, nausea, vomiting and jaundice 1 week; liver and spleen enlarged.
				10/12/34	120	140	60	80	
				10/18/34	120	290	170	120	
				10/30/34	40	395	290	105	Patient improved
46	35	M	.....	8/22/34	38	115	Traces	±115	Two days following appendectomy pneumonia developed in right lower lobe, with jaundice. Patient improved
47	33	F	4½ wks.	9/22/33	38	225	85	140	Jaundice 4½ weeks, clearing up before admission; liver and spleen enlarged.
				10/ 5/33	23	270	135	135	Patient entered toward end of illness
48	26	M	.....	9/ 6/34	48	325	220	105	Anorexia, loss of weight and nausea 5 weeks; vomiting 3 weeks; liver enlarged.
				10/ 8/34	85	290	40	250	
				10/26/34	24	270	170	100	Patient improved
49	45	M	4 days	9/17/34	38	200	45	155	Decompensated rheumatic cardiovalvular disease with jaundice, enlarged liver.
				9/23/34	15	180	115	65	Patient improved with digitalis, diuretics and rest
50	65	M	2 mos.	1/27/31	110	140	30	110	Long-standing chronic cardiovalvular disease, with pulmonary infarcts and jaundice; liver enlarged and tender

TABLE 2.—*Jaundice in Parenchymatous Disease of the Liver—Continued*

Case	Age	Sex	Duration of Jaundice Before Admission	Date	Icterus Index	Cholesterol, Mg. per 100 Cc. of Plasma			Comment
						Total	Ester	Free	
51	42	M	3 wks.	4/14/31	22	215	60	155	Rheumatic cardiovalvular disease with decompensation; enlarged, tender liver and jaundice. Patient improved with digitalis and rest
				4/20/31	15	250	135	115	
52	73	F	.....	5/ 5/31	17	190	50	140	Necropsy: chronic rheumatic cardiovalvular disease; infarction of lung; chronic passive congestion of liver; jaundice
53	38	F	.....	3/16/31	22	120	30	90	Rheumatic cardiovalvular disease; congestive failure; pulmonary infarction; ascites; enlarged liver; jaundice. Patient improved with digitalis and rest
54	21	M	.....	5/ 5/31	36	155	Traces	±155	Rheumatic cardiovalvular disease; congestive failure; pulmonary infarction; enlarged liver; jaundice. Patient improved at first, then became worse and died 6/30/31
55	32	M	.....	4/ 4/31	13	220	50	170	Rheumatic cardiovalvular disease; decompensation; jaundice; enlarged, tender liver. Patient improved with digitalis and rest
				4/18/31	...	220	110	110	
56	42	M	3 days	6/14/31	110	205	30	175	Chancre 6 weeks ago; lingual sore 4 weeks ago; jaundice 3 days; Wassermann reaction 4 plus; acute toxic degeneration of liver in secondary syphilis
				6/20/31	120	165	Traces	±165	
				6/24/31	80	220	45	175	
				7/ 6/31	38	180	75	105	
57	26	M	16 days	1/14/31	75	145	Traces	±145	Four weeks ago arsphenamine therapy followed by nausea and vomiting; increasing dark urine and painless jaundice 16 days ago; acute hepatic degeneration following arsphenamine
				1/20/31	35	290	170	120	
58	30	M	5 wks.	8/26/33	30	170	80	90	Syphilis treated 1 year ago; progressive painless jaundice 5 weeks, lessening in past 2 weeks; liver and spleen palpable. Patient gradually improved
				9/ 1/33	42	250	45	205	
				9/18/33	18	250	145	105	
59	30	M	1 day	10/ 1/31	110	115	40	75	Syphilis; iritis; intravenous antisyphilitic treatment until 3 weeks ago; chills, fever, dark urine; jaundice 1 day; liver enlarged; spleen palpable; toxic hepatic degeneration following arsphenamine. Patient improved
				10/ 5/31	160	195	50	145	
				10/10/31	120	190	55	135	
60	37	F	2½ wks.	10/ 1/31	125	130	25	105	Syphilis; intravenous injections followed by chills, fever and painless jaundice; liver enlarged; spleen palpable; acute toxic hepatic degeneration following arsphenamine. Patient improved slowly
				10/ 8/31	110	150	30	120	
				10/16/31	65	160	35	125	
				10/22/31	50	210	45	165	
61	29	F	4 days	1/29/33	55	185	85	100	Syphilis; arsphenamine therapy; painless jaundice, malaise and fever 4 days; acute toxic hepatitis following arsphenamine
				2/ 6/33	20	190	125	65	
62	21	M	1 day	2/ 9/31	60	150	30	120	Nausea, vomiting and headache 5 days; jaundice 1 day; mucous patches in mouth; secondary syphilis with mucous patches and syphilitic hepatitis; under bismuth therapy jaundice cleared up
63	65	M	1 day	11/ 7/33	35	160	65	95	Necropsy: syphilis; meningococcic arthritis and meningitis; bronchopneumonia; degeneration of liver with atrophy. Patient had received arsphenamine intravenously before admission
				11/11/33	20	155	25	130	
				11/29/33	13	115	Traces	±115	

TABLE 2.—*Jaundice in Parenchymatous Disease of the Liver—Continued*

Case	Age	Sex	Duration of Jaundice Before Admission	Date	Icterus Index	Cholesterol, Mg. per 100 Cc. of Plasma			Comment
						Total	Ester	Free	
64	20	M	4 days	2/13/30	120	120	40	80	Syphilis; intravenous arsphenamine therapy, followed by jaundice; acute toxic hepatic degeneration following arsphenamine. Patient improved
				2/24/30	40	290	185	105	
65	29	M	4 wks.	10/30/30	30	235	70	165	Syphilis; following intravenous therapy jaundice developed; liver enlarged; condition considered acute hepatic degeneration following arsphenamine. Patient improved
				11/ 6/30	12	210	135	75	
66	43	M	.....	6/12/30	8	115	Traces	±115	Syphilis; intravenous injections of arsphenamine followed by fever, vomiting, diffuse dermatitis, no jaundice; patient acutely ill; liver and spleen enlarged
				6/17/30	..	220	45	175	
				6/30/30	10	200	120	80	
67	51	M	5 days	6/27/33	55	250	80	170	Syphilis, treated with bismuth and arsphenamine; nausea and jaundice 5 days; acute hepatic degeneration. Patient improved
68	34	M	7 days	12/23/31	140	235	30	205	Syphilis, treated with intravenous injections; anorexia and drowsiness 2 weeks; jaundice 1 week; liver enlarged and tender; spleen palpable. Patient improved gradually
				12/28/31	80	270	100	170	
				1/ 4/32	35	[illegible]	145	80	
				1/11/32	35	[illegible]	220	100	
69	34	M	4 wks.	2/18/32	270	195	65	130	Syphilis, treated with intravenous injections; malaise, fatigue and jaundice 4 weeks; liver and spleen enlarged. Patient improved; May 1932, well
				2/22/32	200	200	90	110	
				3/ 2/32	80	210	80	130	
70	38	M	13 days	2/ 5/34	150	160	50	110	Syphilis, treated with arsphenamine; fever, anorexia, dizziness and jaundice 13 days; liver enlarged; acute toxic hepatic degeneration following arsphenamine. Patient improved
				2/15/34	45	235	55	180	
				2/19/34	40	260	130	130	
71	50	M	2 days	3/25/32	85	250	85	165	Secondary syphilis with jaundice 2 days; liver enlarged; Wassermann reaction 4 plus; syphilitic hepatitis. Patient improved
72	24	M	1 mo.	8/ 7/34	85	105	Traces	±105	Syphilis; painless jaundice for past month; liver enlarged. Patient improved
				8/13/34	45	125	30	95	
73	33	M	3 wks.	8/ 4/34	85	170	70	100	Syphilis; injections of arsphenamine followed by jaundice. Patient improved slowly
				8/13/34	120	250	130	120	
				8/18/34	110	210	55	155	
74	37	M	12 days	1/19/35	75	160	55	105	Nausea, vomiting and anorexia 1 month; jaundice 12 days; liver and spleen enlarged. Patient improved slowly. Condition considered at first subacute yellow atrophy
				1/26/35	45	160	Traces	±160	
				2/12/35	20	155	25	130	
75	30	F	3 days	1/28/35	88	130	30	100	Weakness, nausea, malaise and fever 6 days; jaundice 3 days; liver enlarged. Patient improved slowly; on follow-up, 4/1/35, well
				2/ 9/35	54	240	70	170	
				2/18/35	40	250	45	205	
76	41	M	2 days	12/30/33	40	250	145	105	Syphilis, treated with arsphenamine; jaundice 2 days; liver enlarged. Patient improved
				1/ 8/34	34	240	135	105	
77	28	M	2 days	3/15/34	50	200	95	105	Syphilis, treated with intravenous injection of arsphenamine; jaundice; liver enlarged; acute toxic hepatic degeneration after arsphenamine. Patient improved
				3/21/34	70	250	70	180	
				4/20/34	20	375	110	265	

TABLE 2.—*Jaundice in Parenchymatous Disease of the Liver—Continued*

Case	Age	Sex	Duration of Jaundice Before Admission	Date	Icterus Index	Cholesterol, Mg. per 100 Cc. of Plasma			Comment
						Total	Ester	Free	
78	48	M	7 days	5/22/33	100	235	125	110	Syphilis; intravenous arsphenamine therapy, followed by jaundice; liver enlarged. Patient improved
79	42	M	6 days	5/15/33	110	260	130	130	Syphilis; intravenous sulfarsphenamine therapy; ingestion of cinchophen, followed by jaundice; liver enlarged. Patient improved
80	43	M	.....	10/ 2/34 10/ 8/34	38 28	325 290	185 130	140 160	Syphilis; rheumatic cardiovalvular disease; patient received neoarsphenamine 10 months ago; jaundiced; large liver and spleen; cardiac decompensation, improved with rest
81	39	M	15 days	10/15/32	100	235	105	130	Syphilis, treated with intravenous injections of arsphenamine; jaundice 15 days; liver enlarged. Patient improved rapidly
82	38	M	7 days	8/31/33 9/18/33	85 25	250 210	135 110	115 100	Syphilis, treated with intravenous injections of neoarsphenamine; malaise, nausea and vomiting 5 weeks; jaundice 1 week; liver enlarged. Patient improved
83	23	M	3 days	10/18/34 11/ 7/34	45 30	310 340	170 265	140 75	Secondary syphilis with lymphadenopathy, rash and jaundice; Wassermann reaction 4 plus. Diagnosis: syphilitic hepatitis. Patient improved under bismuth therapy
84	45	F	1 day	3/17/31 3/25/31	50 30	180 275	80 125	100 150	Syphilis, treated with intravenous injections of neoarsphenamine; vomiting, chills, fever and jaundice; acute hepatic degeneration following neoarsphenamine
85	23	F	6 days	7/22/32	120	210	145	65	Syphilis; intravenous injections of arsphenamine, followed by vomiting and jaundice; acute toxic degeneration of liver following arsphenamine. Patient improved
86	13	M	1 wk.	10/27/34 11/ 5/34	35 15	440 290	250 170	190 120	Sore throat, fever and jaundice 1 week. Twenty other children in institution afflicted. Infectious epidemic catarrhal jaundice. Patient improved rapidly
87	45	M	1 wk.	9/25/34 10/21/34 11/ 5/34 11/17/34	175 150 110 70	290 200 270 320	140 85 145 250	150 115 125 70	Patient received intravenous hypertonic saline solution for thrombo-angiitis obliterans; jaundice developed 1 week later; liver and spleen enlarged. Patient improved
88	57	M	2 wks.	2/ 5/34 2/13/34	50 25	300 270	180 145	120 125	Jaundice following upper respiratory infection; liver enlarged. Patient improved
89	51	M	2 wks.	4/24/34 4/30/34	55 22	200 340	100 235	100 105	Malaise, nausea and vomiting 4 weeks; painless jaundice 2 weeks. Patient improved
90	23	M	4 wks.	2/16/34 2/21/34	65 80	200 210	115 120	85 90	Flatulence and pyrosis 5 weeks; painless jaundice 4 weeks; liver enlarged. Patient improved
91	43	M	11 days	10/ 2/34 10/11/34	70 90	210 230	110 125	100 105	Painless jaundice 11 days; diarrhea 1 day. Patient improved gradually
92	21	M	.....	1/18/34	27	235	145	90	Mild attack of grip and sinusitis, followed by jaundice of short duration. Patient improved rapidly
93	55	F	7 days	6/16/32 6/21/32	105 80	270 250	110 100	160 150	Ingestion of 680 grains (44 Gm.) of cinchophen in 3 months, followed by jaundice. Patient gradually improved

TABLE 2.—*Jaundice in Parenchymatous Disease of the Liver—Continued*

Case	Age	Sex	Duration of Jaundice Before Admission	Date	Icterus Index	Cholesterol, Mg. per 100 Cc. of Plasma			Comment
						Total	Ester	Free	
94	20	M	6 days	5/10/33	100	270	155	115	Pararectal abscess 3 weeks; jaundice 6 days; liver enlarged. Patient improved rapidly
				5/22/33	45	220	130	90	
95	26	M	4 days	6/ 7/32	80	235	150	85	Malaise, nausea and weakness 2 weeks; jaundice 4 days; liver and spleen enlarged. Patient improved rapidly
				6/13/32	30	215	115	100	
96	37	F	10 days	3/14/32	85	290	155	135	Anorexia, pyrosis and nausea 2 weeks; jaundice 10 days; liver enlarged. Patient improved slowly
				3/21/32	145	175	80	95	
				4/25/32	36	290	155	135	
97	15	M	7 days	12/ 5/31	40	340	180	160	Anorexia, nausea and epigastric distress 10 days; jaundice 7 days; liver enlarged. Patient improved rapidly
				12/10/31	25	290	170	120	
98	14	M	6 days	11/ 2/31	45	310	170	140	Weakness and fatigue 2 weeks; jaundice 6 days; liver enlarged. Patient improved rapidly
				11/ 9/31	23	280	115	165	
99	23	F	2 days	10/13/31	85	130	60	70	Nausea and jaundice 2 days; liver and spleen palpable. Patient improved
				10/22/31	45	200	80	120	
100	26	M	7 days	5/23/33	85	170	70	100	Progressive painless jaundice 7 days; liver and spleen palpable. Patient improved gradually
				6/16/33	50	280	200	80	
101	27	M	3 days	12/24/32	100	190	95	95	Nausea, vomiting, anorexia and jaundice 3 days. Patient improved gradually
				1/ 5/33	160	140	90	50	
				1/11/33	75				
102	41	M	4 days	1/12/33	180	170	80	90	Anorexia, pyrosis and jaundice 4 days; liver and spleen enlarged. Patient improved slowly
				1/20/33	45	340	130	210	
103	14	F	36 hrs.	3/10/33	60	205	100	105	Nausea, vomiting, fever and pain in right upper quadrant of abdomen 9 days; jaundice 36 hours. Condition probably gastroduodenitis with jaundice. Patient improved rapidly
				3/20/33	17	270	170	100	
104	51	M	3 days	6/18/34	60	290	145	145	Arthritic attacks for months; patient took heavy doses of drugs; jaundice 3 days; galactose test positive. Patient improved
				6/22/34	70	230	95	135	
				7/20/34	55	395	235	160	
105	8	M	6 days	6/15/34	80	300	135	165	Decompensated rheumatic cardiovalvular disease. Patient improved with rest
				6/19/34	54	290	70	220	
				6/25/34	20	310	135	175	
106	35	F	5 days	12/31/34	90	235	95	140	Infectious mononucleosis, with jaundice developing 5 days before admission. Patient improved
				1/ 5/35	56	275	80	195	
				1/10/35	20	250	135	115	
107	27	M	3 days	3/15/34	35	310	155	155	Jaundice following alcoholic spree; liver and spleen enlarged. Patient improved
				3/26/34	8	250	145	105	
108	8	M	3 days	5/14/34	35	340	155	185	Anorexia, nausea, vomiting and jaundice 3 days; several children in institution suffered similar attack. Patient improved
109	25	M	.....	10/23/34	45	220	125	95	Nausea, vomiting and anorexia 1 week; jaundice on admission. Patient improved
				11/ 3/34	20	340	185	155	
110	46	M	2 wks.	10/26/34	125	385	310	75	Nausea, vomiting, generalized aches and jaundice 2 weeks. Patient improved
				11/12/34	50	310	220	90	
111	13	M	.....	10/15/34	45	250	140	110	Sister and brother had jaundice preceding patient's illness; liver enlarged. Patient improved

COMMENT

As early as 1918, Feigl [30] reported low values of cholesterol ester in a study of the blood lipoids in acute yellow atrophy, but he did not attach any special significance to the observations. It was not until 1926 that a clinical interpretation of the cholesterol partition of the blood in diseases of the liver was reached. Thannhauser and Schaber [31] found not only low values of cholesterol ester in hepatic diseases but also a total disappearance of the ester from the blood in acute yellow atrophy. They called this phenomenon *Esterstürz* and believed that it represented a disturbance in the ability of the liver to regulate the level of the blood cholesterol and its esters. Their findings were corroborated by Adler and Lemmel,[14] Wendt,[32] Mancke,[33] Epstein,[7b] Geill,[34] Stroebe,[16] and Mjassnikow.[17]

Adler and Lemmel were able to show in a large series of cases that a fall of the cholesterol ester of the blood plasma occurred in parenchymatous disease of the liver. They demonstrated this by comparing the values of the ester with the results of other tests of hepatic function and concluded that the abnormal cholesterol picture usually parallels disturbances in the other functions of the liver. Most of the other authors cited agreed that the liver plays an important rôle in cholesterol metabolism and that the cholesterol partition reflects disturbances in hepatic function, the exact mechanism of which is not thoroughly understood.

Opposed to this view are the reports of Bürger and Habs, Stern and Suchantke, and Gardner and Gainsborough, who expressed the belief that the drop in ester is merely a result of the failure of fat resorption because of the absence of bile from the intestines. In answer to this objection we quote our observations of normal and even markedly increased values of ester in cases of obstructive jaundice in which no bile was present in the intestines; also the markedly lowered values of ester in parenchymatous diseases of the liver in which bile is present in the stools in appreciable amounts. It is therefore safe to assume that the liver must be actively involved in cholesterol metabolism, although the rôle of the fat absorption is an important one.

Animal experimentation has given divergent results. Gebhardt [35] found that there was a marked fall in the total and ester cholesterol in the blood in dogs with Eck fistula and in hepatectomized dogs, whereas

30. Feigl, J.: Biochem. Ztschr. **86**:1, 1918.

31. Thannhauser, S. J., and Schaber, H.: Klin. Wchnschr. **5**:252, 1926.

32. Wendt, H.: Klin. Wchnschr. **8**:1215, 1929.

33. Mancke, R.: Deutsches Arch. f. klin. Med. **170**:358, 1931.

34. Geill, T.: Hospitalstid. **74**:1094, 1931.

35. Gebhardt, F.: Verhandl. d. deutsch. Gesellsch. f. inn. Med. **43**:215, 1931.

Enderlen, Thannhauser and Jenke [36] reported increased values under similar conditions. Moreover, Mann [37] found no significant changes in the blood cholesterol before and at various periods after removal of the liver. Recently work has been done by Hawkins and Wright [27] on the fluctuations of the blood plasma cholesterol due to injury of the liver and obstruction of the bile duct in dogs. They have shown that hypocholesterolemia with dissociation of the normal ratio of esterified to total cholesterol is related to chronic injury of the liver caused by chloroform, and that hypercholesterolemia eventually developed after prolonged biliary obstruction. They also found in dogs with biliary fistulas that the absence of bile in the intestine with faulty fat absorption does not cause the development of hypocholesterolemia with dissociation of the ester ratio. We have had opportunity to make similar observations in dogs, using both chloroform and carbon tetrachloride as hepatic poisons.

We have observed in our series that the total cholesterol of the blood in jaundice due to parenchymatous disease of the liver does not parallel the hyperbilirubinemia. This divergence stands in bold relief to the association of hypercholesterolemia and hyperbilirubinemia seen in most instances of obstruction of the biliary passages. Usually the cholesterol level in cases of hepatic damage is normal or even subnormal, although in a number of cases a slight rise is observed. This increase never reaches that of the cholesterol in cases of obstructive jaundice. Moreover, those cases of parenchymatous disease of the liver in which the initial cholesterol figures are high usually have a favorable termination in spite of the severe degree of jaundice and apparently serious clinical outlook.

The study of the cholesterol esters has given interesting results. In the more severe cases of hepatic damage the cholesterol ester is initially lowered or is present in minute amounts only and remains low when the outcome is fatal. It rises slowly to reach normal proportions when gradual improvement occurs in the course of the disease. In the less severe instances the reduction in the ester at the beginning is not marked, and soon a gradual rise to normal occurs. In some cases the cholesterol levels do not vary from the normal. These may be cases in which the damage is mild or in which the process is in the reparative stage. A few of these cases of jaundice may represent what Klemperer ascribed to ascending or descending cholangiolitis rather than to hepatic damage. A hypercholesterolemia, both total and ester, at times reaching fairly high levels, was found in many instances with regeneration and healing.

36. Enderlen, E.; Thannhauser, S. J., and Jenke, M.: Arch. f. exper. Path. u. Pharmakol. **120**:16, 1927.

37. Mann, F.: Modified Physiologic Processes Following Total Removal of Liver, J. A. M. A. **85**:1472 (Nov. 7) 1925.

The hypercholesterolemia may last for one month after complete recovery.

The cholesterol ester seems thus to afford a useful measure of the degree of hepatic damage, falling to low levels with severe degeneration and rising to normal or even above normal with improvement. It has helped materially as an aid in prognosis. Patients with an apparently hopeless clinical outlook and rising ester levels have improved and, conversely, those with apparently mild disease and steadily falling ester levels have gone on to yellow atrophy of the liver and death.

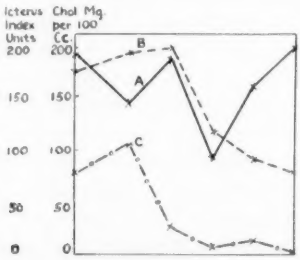

Chart 9.—A typical case of acute yellow atrophy, with total cholesterol (*B*) and ester (*C*) gradually falling with increasing severity of the disease. The ester was present only in traces toward the end. *A* is the icterus index.

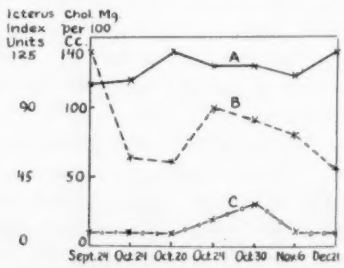

Chart 10.—A case of yellow atrophy in the subacute form. The total cholesterol (*B*) and ester (*C*) remained low throughout the course of the disease. The ester, on repeated determinations, was present only in traces. *A* is the icterus index.

ATROPHY OF THE LIVER

The significance of the cholesterol ester of the blood in acute hepatic damage as an index of the degree of damage and of the prognosis is best visualized in so-called atrophy of the liver. In table 3 are presented 13 cases of acute, subacute or chronic yellow atrophy with coarse nodular cirrhosis which came to postmortem investigation. Of these, the condition was acute in 5, subacute in 5 and chronic, with nodular cirrhosis, in 3.

The outstanding feature in all the cases was the marked fall of the cholesterol ester, which remained very low throughout the entire fatal course. A steadily dropping ester or the absence of cholesterol ester from the blood in a case of jaundice is of serious import, even when the clinical condition of the patient seems satisfactory.

TABLE 3.—*Yellow Atrophy of the Liver*

Case	Age	Sex	Duration of Jaundice Before Admission	Date	Icterus Index	Cholesterol, Mg. per 100 Cc. of Plasma		
						Total	Ester	Free
1	41	M	3 days	1/27/33	110	180	20	160
				1/30/33	...	120	Trace	±120
2	37	F	3 wks.	10/16/30	100	175	65	110
				10/27/30	140	105	Trace	±105
3	59	M	1 wk.	1/14/31	150	100	Trace	±100
				1/18/31	...	50	Trace	± 50
4	8	F	2½ wks.	10/30/31	185	185	80	105
				11/ 4/31	135	195	95	100
				11/14/31	190	200	30	170
				11/23/31	230	140	..	...
				12/14/31	90	135	..	...
				12/21/31	150	70	..	...
				1/ 4/32	90	115	Trace	±115
				2/15/32	180	100	20	80
				3/ 4/32	...	80	Trace	± 80
5	57	F	1 wk.	10/ 9/33	200	210	125	85
				10/13/33	270	170	20	150
				10/16/33	...	200	30	170
				10/25/33	250	140	25	115
				10/30/33	235	125	Trace	±125
6	26	M	4 wks.	5/23/31	200	140	Trace	±140
				5/26/31	...	100	Trace	±100
7	52	F	2 wks.	6/24/30	150	130	Trace	±130
8	12	F	20 mos.	4/13/31	120	60	Trace	± 60
				4/17/31	160	70	Trace	± 70
				4/23/31	120	65	0	65
				5/19/31	110	Trace	0	Trace
				5/26/31	...	80	0	80
9	16	F	1 mo.	6/11/31	95	150	55	95
				7/ 6/31	90	110	Trace	±110
10	35	F	9 wks.	3/17/31	75	120	40	80
				3/23/31	70	90	35	55
				3/31/31	..	100	Trace	±100
				4/ 7/31	75	85	0	85
				4/16/31	35	90	0	90
11	54	M	5 days	2/13/35	75	150	30	120
				2/15/35	75	155	Trace	±155
				2/16/35	..	115	Trace	±115
12	23	M	4 days	1/25/35	150	190	40	150
				1/28/35	140	165	Trace	±165
				1/29/35	...	200	20	180
13	18	F	3 yrs.	9/24/31	100	140	Trace	±140
				10/14/31	100	65	Trace	± 65
				10/20/31	125	60	Trace	± 60
				10/24/31	...	100	20	80
				10/30/31	...	105	30	75
				11/ 6/31	110	90	Trace	± 90
				12/21/31	125	65	Trace	± 65

The total cholesterol of the blood showed the same relationship to the hyperbilirubinemia as in catarrhal or toxic jaundice, only to an exaggerated degree—namely, lowered total cholesterol in spite of considerable hyperbilirubinemia, the icteric index in one case reaching 270. The total cholesterol values were the lowest we have observed, at times being so low that they could not be measured by the method employed.

ATROPHIC CIRRHOSIS OF THE LIVER

Thirty cases of atrophic cirrhosis of the liver (Laënnec) were studied, of which 17 were examined at necropsy and one at operation. The others were considered typical instances of Laënnec's cirrhosis, and in each several of the following observations were recorded: considerable imbibition of alcohol over many years, hematemesis, melena, enlargement and induration of the liver, palpable spleen, evidence of collateral cutaneous circulation, and ascites with repeated paracenteses.

In any study of atrophic cirrhosis of the liver one must recognize at which stage of the disease the patient is seen. These stages represent, respectively, the result of portal obstruction, a superimposed hepatitis in the course of the cirrhosis, or terminal failure of the liver

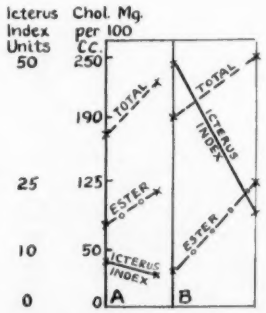

Chart 11.—Two typical cases of atrophic cirrhosis of the liver. In *A*, in which portal obstruction was present without jaundice, the cholesterol partition was normal. In *B*, in which there was jaundice due to a superimposed hepatitis, the cholesterol ester was low. With improvement and diminution of the jaundice, the ester gradually rose to normal.

expressed in cholemia. Jaundice in the course of atrophic cirrhosis of the liver is uncommon and, when present, is usually slight. Unless an unrelated obstruction to the biliary passages is present, icterus is usually indicative of a complicating hepatic degeneration.

There were 13 cases of atrophic cirrhosis of the liver in which no jaundice occurred and in which the consequences of the portal obstruction predominated. The blood cholesterol partition was approximately normal with a slight occasional diminution of the cholesterol ester. In 3 cases (21, 22, 27) the postmortem examination revealed, in addition to atrophic portal cirrhosis, a primary carcinoma of the liver. Here the cholesterol figures do not conform with those for the other cirrhoses, perhaps because of the complicating carcinoma.

The remaining 14 cases of atrophic cirrhosis of the liver presented jaundice due either to a superimposed intercurrent degeneration of the

TABLE 4.—*Atrophic Cirrhosis of the Liver*

Case	Age	Sex	Duration of Jaundice Before Admission	Date	Icterus Index	Cholesterol, Mg. per 100 Cc. of Plasma			Comment
						Total	Ester	Free	
1	66	F	.....	2/26/31	11	205	100	105	Necropsy: atrophic portal cirrhosis
2	64	M	.....	12/22/31	4	225	140	85	Necropsy: atrophic portal cirrhosis
3	60	M	.....	9/22/32	15	220	145	75	Chronic alcoholism; ascites; paracentesis abdominis — 7,000 cc.; liver hard and irregular; urine — urobilin
4	46	M	1 wk.	1/15/32	20	215	110	105	Necropsy: atrophic portal cirrhosis
5	60	M	.....	1/ 2/35	12	215	50	165	Ascites; collateral circulation; paracentesis abdominis; liver enlarged to umbilicus; spleen palpable 3 fingerbreadths; urine, urobilin; Takata-Ara reaction strongly positive
				1/18/35	9	200	65	135	
6	53	M	.....	12/11/34	22	270	45	125	Recurrent ascites; multiple paracenteses
				12/18/34	..	300	100	200	
				12/21/34	28	290	195	95	
				12/26/34	..	340	165	175	
7	54	M	.....	4/19/34	6	160	95	65	Necropsy: atrophic portal cirrhosis
8	42	M	.....	7/ 5/34	8	535	160	375	Necropsy: atrophic portal cirrhosis
9	30	M	.....	4/29/30	..	190	90	100	Chronic alcoholism; ascites; esophageal varices
				5/10/30	10	160	50	110	
10	61	F	.....	3/ 8/30	8	210	70	140	Periodic excessive alcoholism; enlarged hard liver, 4 fingerbreadths below costal margin
11	64	M	.....	1/17/30	22	155	40	115	Necropsy: atrophic portal cirrhosis with adenomas
12	40	F	6 wks.	2/ 5/30	..	195	100	95	Chronic alcoholism; jaundice occurred after alcoholic debauch 6 weeks before admission; liver and spleen enlarged; urine, urobilin
				2/13/30	25	210	95	115	
13	33	M	.....	8/ 7/30	7	130	70	60	Operation: cirrhosis of liver. Splenectomy
14	62	M	.....	9/21/34	20	190	55	135	Persistent ascites for 5 months prior to admission. Paracentesis abdominis performed 5 times. Urine — urobilin
				10/ 5/34	20	150	40	110	
15	63	F	.....	9/18/30	16	150	65	85	Necropsy: atrophic portal cirrhosis
16	38	F	.....	10/26/32	9	170	70	100	Recurrent ascites; paracentesis abdominis performed 6 times — 11,000 cc. of clear fluid removed during last tap; collateral circulation; urine — urobilin
				11/30/32	6	220	120	100	
17	45	M	.....	3/25/31	12	250	60	190	Necropsy: atrophic portal cirrhosis
				4/11/31	10	270	110	160	
18	48	M	.....	1/29/31	45	120	45	75	Collateral circulation; recurrent ascites with paracentesis abdominis; large spleen; urine — urobilin
19	53	M	3 wks.	2/29/32	120	235	65	170	Necropsy: atrophic portal cirrhosis
				3/ 5/32	70	180	50	130	
20	42	F	10 days	2/15/32	140	120	35	85	Necropsy: portal cirrhosis with areas of hepatic degeneration
21	61	M	1 mo.	8/28/31	50	290	120	170	Necropsy: atrophic portal cirrhosis; primary carcinoma of liver
				9/ 4/31	37	265	50	215	
				9/15/31	100	310	90	220	
22	61	M	6 days	12/ 6/32	150	210	55	155	Necropsy: atrophic portal cirrhosis; primary carcinoma of liver
23	36	F	2 mos.	9/ 8/31	40	185	35	150	Necropsy: atrophic portal cirrhosis

TABLE 4.—*Atrophic Cirrhosis of the Liver—Continued*

Case	Age	Sex	Duration of Jaundice Before Admission	Date	Icterus Index	Cholesterol, Mg. per 100 Cc. of Plasma			Comment
						Total	Ester	Free	
24	50	M	2 wks.	2/ 2/32	36	140	40	100	Increasing ascites 3 weeks, icterus 2 weeks prior to admission; cholemia at time of death; urine — urobilin
25	52	M	.....	2/28/33	..	60	Tr.	±60	Necropsy: atrophic portal cirrhosis; focal areas of acute degeneration of liver
				3/13/33	27	100	Tr.	±100	
				3/16/33	50	55	Tr.	±55	
26	49	M	8 mos.	9/15/33	23	105	Tr.	±105	Recurrent ascites; icterus 8 months prior to admission; paracenteses abdominis 18 times; cholemia at time of death; urine — urobilin
27	62	M	.....	12/ 3/32	35	420	270	150	Necropsy: atrophic portal cirrhosis; primary carcinoma of liver
28	46	M	6½ mos.	2/19/31	45	310	170	140	Necropsy: atrophic portal cirrhosis
29	60	F	2 mos.	1/ 2/34	35	250	195	55	Necropsy: atrophic portal cirrhosis with adenomas
				2/ 9/34	40	230	30	200	
				2/20/34	65	165	30	135	
				3/29/34	38	190	80	110	
				4/ 9/34	50	170	55	115	
30	38	M	.....	1/ 9/33	7	150	40	110	Chronic alcoholism; ascites; paracentesis abdominis — 19,000 cc.; urine — urobilin

liver or to cholemia in the terminal stage of cirrhosis. In this group of Laënnec's cirrhosis with jaundice we observed that the cholesterol partition behaved as in the primary hepatic degenerations. The total cholesterol was subnormal and the cholesterol ester considerably lowered or even entirely absent. The cholesterol ester rose to approximately normal values as clinical improvement occurred (table 4).

The functions of the liver tend to remain normal in the type of hepatic disease exemplified by atrophic portal cirrhosis in which the evolution is slow, the distribution is periportal and regeneration is present. The deviations are present when superimposed hepatitis or terminal cholemia occurs. The total and ester cholesterol showed practically no variations from normal in the cases in which jaundice was absent and in which the mechanical obstruction to the portal circulation produced the outstanding symptoms. When jaundice supervened, the cholesterol partition was similar to that seen in acute degeneration of the liver. The normal blood cholesterol picture in nonjaundiced patients with atrophic portal cirrhosis agrees with previous reports of Adler and Lemmel and of Epstein.

NONOBSTRUCTIVE DISEASE OF THE BILIARY TRACT

A group of 30 unselected cases of acute or chronic cholecystitis and cholelithiasis without obstruction in which operation was performed are presented in table 5. Contrary to accepted belief, the cholesterol of the blood plasma was not regularly elevated. In only 8 cases did the total cholesterol reach 300 mg. in 100 cc. of plasma. The cholesterol

was below 200 mg. in 7 instances, and in the remaining ones it was between 200 and 300 mg.

The cholesterol ester retained its normal relationship to the total cholesterol in 18 instances. In other instances there was no absolute rise or fall, but the relative proportion remained low. Rothschild and Rosenthal,[38] Campbell,[39] Adler and Lemmel [14] and others also found very little change in the blood cholesterol picture in uncomplicated nonobstructive disease of the biliary tract. Recently Colp, Doubilet and

TABLE 5.—*Nonobstructive Disease of Biliary Tract*

Case	Age	Sex	Icterus Index	Cholesterol, Mg. per 100 Cc. of Plasma		
				Total	Ester	Free
1	24	F	8	250	120	130
2	31	F	7	230	115	115
3	30	M	13	235	115	120
4	45	F	8	325	170	155
5	38	F	30	250	175	75
6	45	F	8	235	95	140
7	46	F	6	360	250	110
8	30	F	13	200	55	145
9	50	F	16	270	85	185
10	49	F	16	240	60	180
11	39	F	8	530	265	265
12	45	F	12	280	110	170
13	56	F	12	325	180	145
14	50	F	10	165	70	95
15	43	F	8	290	70	220
16	39	F	9	575	150	425
17	66	F	6	125	60	65
18	42	F	5	135	65	70
19	34	F	10	350	280	70
20	31	F	8	235	110	125
21	35	F	5	180	125	55
22	31	F	8	135	105	30
23	27	F	6	280	110	170
24	38	F	5	270	150	120
25	32	F	10	300	155	145
26	37	F	5	225	145	80
27	19	F	6	230	125	105
28	58	F	35	175	45	130
				160	85	75
29	45	F	6	340	120	220
30	42	F	5	175	90	85

Gerber [40] were able to study the pathologic changes of the liver in nonobstructive disease of the biliary tract by means of the punch biopsy at operation. Their studies confirm the previous beliefs that little or no damage to the liver occurs in nonobstructive disease of the biliary tract.

SUMMARY

We have been purposely careful to avoid the term "liver function test" and have considered the significance of the variations in the plasma cholesterol and ester in diseases of the liver and biliary passages. There are numerous instances of elevated or depressed levels of the blood cholesterol in other diseases, which cannot be considered an expression of a disturbance of hepatic or biliary function. Low levels of total and

38. Rothschild, M. A., and Rosenthal, N.: Am. J. M. Sc. **152**:394, 1916.
39. Campbell, J.: Quart. J. Med. **18**:123, 1924.
40. Colp, R.; Doubilet, H., and Gerber, I. E.: Ann. Surg. **102**:202, 1935.

ester cholesterol are observed in some cases of severe infection—such as bacterial endocarditis, cystopyelonephritis, necrotizing infections and pyelophlebitis. With the subsidence of the infection the values for cholesterol again approach normal. Likewise in ulcerative colitis, sprue, severe diarrheas, pernicious anemia, severe secondary anemias and exophthalmic goiter the blood cholesterol partition may be disturbed.

However, the determination of the blood cholesterol and ester has enabled us to improve our accuracy in the diagnosis and prognosis of hepatic and biliary diseases. In obstructive jaundice hypercholesterolemia is usually encountered, affecting both the free and the ester fractions, which parallels the degree of hyperbilirubinemia. With the relief of the obstruction and the lessening of the jaundice, the cholesterol gradually returns to normal. In some instances—long-standing biliary stasis, superimposed infections of the biliary passages, cachexia and other complications—the cholesterol level may not rise above normal.

In jaundice occurring in acute degeneration of the liver blood cholesterol does not rise with the bilirubin, but usually remains normal or subnormal. This divergence between the degrees of blood cholesterol and blood bilirubin in parenchymatous diseases of the liver contrasts sharply with the parallelism between the hyperbilirubinemia and hypercholesterolemia in obstructive jaundice and usually affords a means of differentiation between the two types of jaundice.

The cholesterol ester is usually lowered in acute degeneration of the liver and mirrors the severity of the damage. In rapidly fatal cases the ester is low or even absent throughout the course of the disease. In the cases in which the disease is less severe the initial low values of ester gradually rise to normal with improvement, and in the cases in which the disease is mild the initial levels are only moderately depressed.

In atrophic cirrhosis of the liver (Laënnec) the blood cholesterol partition remains normal except when jaundice supervenes in the course of an intercurrent acute hepatic degeneration or terminal cholemia. In these instances the blood cholesterol partition behaves as in the primary degenerations of the liver.

In cholecystitis and cholelithiasis with no obstruction to the biliary outflow the blood cholesterol levels are normal or insignificantly elevated.

In using the cholesterol partition as an aid in the diagnosis and prognosis of diseases of the liver and biliary tract repeated determinations during the course of the illness give an indication of the trend and are therefore of much more value than a single determination. In evaluating the significance of a single determination of the cholesterol partition, erroneous conclusions can usually be avoided, just as with the Wassermann test, if the result is considered in the light of the clinical sequence of events and if allowances are made for the stages of the disease and the possible existence of infections and of extrahepatic diseases which may also influence the cholesterol level of the blood.

ACTIONS OF DIURETIC DRUGS AND CHANGES IN METABOLITES IN EDEMATOUS PATIENTS

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SAN FRANCISCO

In previous papers I have discussed the concurrent changes in the output of urine and in the blood and urinary metabolites of animals and edematous patients treated with diuretic drugs.[1] The following drugs produced increases in the output of urine and in the chloride content of the blood and urine: sodium bismuth tartrate, theophylline, merbaphen and salyrgan. Bismuth caused the same effects in normal and chloride-saturated rabbits but much less pronounced changes in those deprived of chloride. In edematous patients the increase in the amount of urinary urea and of uric acid after the administration of bismuth paralleled the diuresis, and the concentration of these metabolites, the dilution of the urine. The hemoglobin, sugar, urea and uric acid contents of the blood showed no changes, or only negligible ones, after the administration of bismuth.

The effects on the chloride content during diuresis due to digitalis differed. This drug reduced the chloride content of the blood and at the same time increased the chloride content of the urine. The effects of spontaneous diuresis without the use of drugs were identical with those of diuresis due to digitalis. These various results suggested differences in the seat and mechanism of the diuretic actions. That is, the purine and the metallodiuretic drugs appeared to mediate the diuretic effects through a direct action on the tissues, in general, while digitalis acted indirectly by way of a circulatory improvement; that is, the purine and the metallodiuretic drugs seemed to act by virtue of the mobilization of salt, while digitalis and also the spontaneous removal of water did not. As the data on theophylline, merbaphen and salyrgan were incomplete, the work was continued with special attention to early

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1. Stockton, A. B.: Proc. Soc. Exper. Biol. & Med. **27**:721, 1930; Arch. internat. de pharmacodyn. et de thérap. **41**:52, 1931; Bismuth Diuresis and the Blood and Urinary Changes Under Clinical Conditions, Arch. Int. Med. **50**:142 (July) 1932; Diuretic Effects and Changes in Blood and Urinary Metabolites After Digitalis in Normal and in Edematous Persons, ibid. **50**:480 (Sept.) 1932.

changes in the amount of chlorides in the blood and urine. For if it could be shown that increase in the chloride content of the blood preceded increase in the output of urine and in the chloride content of the urine this would be evidence of the mobilization of chlorides from the tissues, in support of the so-called theory of tissue diuresis. Such evidence is offered in this report, which presents the completed data on these diuretic drugs.

METHODS

Seventeen edematous patients were studied. Fourteen had edema due to cardiac decompensation, and three had portal cirrhosis with ascites and pitting edema of the legs. The patients were divided into three groups: Six received theophylline, six merbaphen and five salyrgan. Each group contained one patient with portal cirrhosis.

All the patients were kept at absolute rest in bed for the duration of the observations. They were given diets low in salt (2 Gm. daily) and a constant daily intake of 1,200 cc. of fluids. Specimens of urine for analysis were collected at intervals of from fifteen minutes to four hours during the first twenty-four hours and then for variable periods as long as the diuretic action lasted. Specimens of blood were obtained during the control periods at four hour intervals and after the administration of drugs at the same time the specimens of urine were collected.

The control periods varied from patient to patient, but in every case they continued until the intake of fluid, the output of urine and the chloride contents of the blood and urine remained nearly constant for three days.

Theophylline was given orally in capsules immediately after breakfast in total doses ranging between 0.6 and 1.5 Gm. Merbaphen and salyrgan were administered intravenously, the total doses ranging between 0.5 and 2 cc.

The chloride content of the blood was estimated by the method of Austin and Van Slyke [2] and that of the urine by the Seelman-Volhard method.[3] The results are presented in charts 1 to 3 as average percentage changes from the control periods.

EFFECTS OF VARIOUS DRUGS

Theophylline.—After the administration of theophylline the onset of diuresis occurred in four hours and continued for about thirty-five hours. Diuresis was at its peak in twenty-two hours. The concentration of chloride in the urine reached a maximum in six hours and again in twenty-three hours. The lowest concentration occurred during the peak of diuresis. The minute output of sodium chloride paralleled almost exactly the curve of diuresis. The chloride content of the blood was at first depressed; it had returned to normal at the end of fourteen hours, and it then reached a maximum in eighteen hours, just preceding the maximum diuresis. At the end of twenty-seven hours, it fell to normal, as the output of urine returned toward normal.

Merbaphen.—Diuresis (chart 2) began two hours after the administration of merbaphen reached its maximum in five and thirteen hours and persisted in large volume for about sixteen hours. Following this marked diuresis the output of urine remained somewhat above that of the control period for about fourteen hours. The total duration of diuresis was about thirty hours. The concentration

2. Austin, J. H., and Van Slyke, D.D.: J. Biol. Chem. **41**:345, 1920.

3. Seelman, J. J.: J. Lab. & Clin. Med. **1**:444, 1916.

of chloride in the urine was increased moderately from the beginning of diuresis and was sustained with some fluctuations during the marked diuresis of the first sixteen hours. The highest concentration occurred during the time of maximum diuresis at the end of thirteen hours. The minute output of urinary chloride closely paralleled the diuresis. The chloride content of the blood began to increase

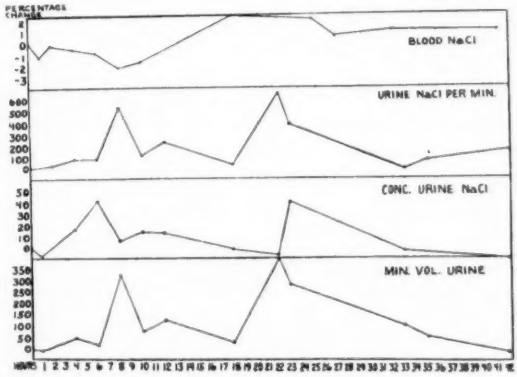

Chart. 1—Average percentage of change in the output of urine and in the chloride content of the blood and urine of patients receiving theophylline.

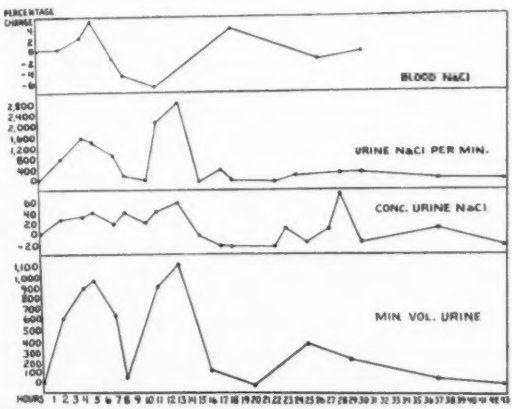

Chart 2.—Average percentage of change in the output of urine and in the chloride content of the blood and urine of patients receiving merbaphen.

two hours after the administration of the drug. It reached a maximum in five hours, when diuresis was at its height, and then fell, being below the control level at the end of eleven hours. At the end of eighteen hours a second marked elevation occurred, which lasted for about three hours, with somewhat delayed increases in the output of urine and the chloride content of the urine.

Salyrgan.—Diuresis due to salyrgan (chart 3) began at the end of one hour, reached a maximum in five hours and had returned almost to the control level after twenty hours. The chloride contents of the blood and urine increased in the same way as after the administration of merbaphen, but the amplitude of the increases was greater. The maximum increase in the chloride content of the blood occurred three hours before the maximum increase in diuresis, thus suggesting that diuresis depended on the mobilization of chloride from the tissues. On the whole, salyrgan appeared to be somewhat more effective than merbaphen, but qualitatively it acted the same.

Comment.—Rearrangement of the patients into groups according to the order of administration of the diuretic drug, i. e., before or after the previous administration of a diuretic drug, demonstrated only

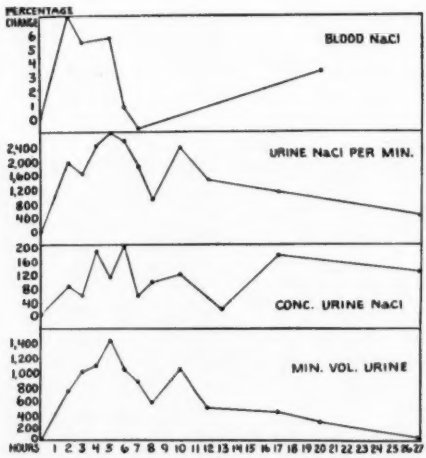

Chart 3.—Average percentage of change in the output of urine and in the chloride content of the blood and urine of patients receiving salyrgan.

that the average diuretic response was greater after the administration of the first diuretic drug, regardless of the kind. That is to say, the diuretic response to salyrgan was greatest when the drug was used first, and the response was less when it was given after another diuretic drug or when a previous dose of salyrgan had been administered. In making these comparisons, ample time for recovery was always permitted between the giving of diuretic drugs to a patient, the output of urine being allowed to return to the control level and remain there for a minimum of forty-eight hours before another diuretic drug was given. Therefore, the decrease in the response must have been due to the decrease in the quantity of edema fluid in the patient. Any patient who was refractory to one diuretic drug was usually refractory to all.

VARIOUS ADJUVANTS WITH DIURETIC DRUGS

The increased response to diuretic drugs following the oral administration of ammonium nitrate, ammonium chloride, calcium chloride,[4] magnesium sulfate, sodium sulfate,[5] potassium chloride,[6] decholin sodium,[7] urea, hydrochloric acid [8] and other substances has been described by many investigators. It has been claimed that any substance which increases the acidity of urine will increase diuresis. Some investigators have claimed that the diuresis is increased by compounds which contain the chlorine ion in the absence of sodium, such as ammonium chloride, calcium chloride, potassium chloride and hydrochloric acid.

Of the patients studied six were given ammonium chloride in doses of 2.6 Gm. daily; two were given 5 Gm. of potassium chloride daily and two were placed on a salt-free diet. The group receiving ammonium chloride showed an average increase of 16.2 per cent (with a range of from + 44.8 to — 1.2 per cent) in diuresis. The concentration of chloride in the urine was increased 11.2 per cent (with a range of from + 22.7 to 0 per cent). The daily output of chloride in the urine also was increased to 42.6 per cent (with a range of from + 90 to + 6 per cent). The chloride content of the blood remained practically unchanged, showing an increase of only 0.2 per cent at the time of the increase in diuresis.

Two patients receiving potassium chloride also showed an increase in the output of urine as long as the salt was given, i. e., 78.1 per cent above the control level. The daily output of chloride increased 37.3 per cent, but the concentration in the urine fell 10.9 per cent. The chloride content of the blood increased 2.7 per cent, which was not significant, although the increase occurred at the time of the increase in diuresis.

Two patients placed on a salt-free diet also showed a permanent increase in the output of urine. During the first ten days this increase averaged 77.2 per cent, and during the second ten day period, 56.1 per cent. The daily output of chloride fell 1.8 per cent, and the concentration of chloride decreased 58.2 per cent. The chloride content of the blood showed a small decline, of 2.4 per cent.

It is apparent from the results described that increases in diuresis followed the administration of the chlorine ion when it was not combined with sodium. Restricted intake of sodium and of chlorine likewise resulted in diuresis. Torbert and Cheney [9] were able to produce in

4. Misumi, K.: J. Biochem. **5**:417, 1925. Keith, N. M.: Am. J. Physiol. **68**:80, 1924.

5. Bloch, E.: Ztschr. f. klin. Med. **106**:733, 1927.

6. Barker, M. H.: Edema as Influenced by a Low Ratio of Sodium to Potassium Intake, J. A. M. A. **98**:2193 (June 18) 1932.

7. Bix, H.: Wien. klin. Wchnschr. **41**:1080, 1928.

8. Herrmann, G.; Schwab, E. H.; Alvarez, J. A., and Cate, M. E.: Proc. Soc. Exper. Biol. & Med. **30**:1375, 1933.

9. Torbert, H. C., and Cheney, G.: Reduction in Colloidal Osmotic Pressure of Blood Serum After Salt Ingestion, J. A. M. A. **106**:683 (Feb. 29) 1936.

normal subjects a frank pitting edema of the extremities by administering large quantities of sodium chloride and water. Wiley and his co-workers noted the retention of fluids after the administration of sodium bicarbonate. Loeb,[10] Lashmet,[11] Barker [12] and many others have shown the relation of the retention of sodium chloride to the edema occurring in Bright's disease by use of the salt-free diet. Therefore, the sodium ion appears to play an important part in the retention of fluid of edema and ascites. Further evidence of its importance is provided by the following results, which indicate storage of sodium chloride in edema and ascitic fluid of edematous patients.

*Comparative Clinical Effects of Diuretic Drugs**

	Theophylline	Merbaphen	Salyrgan	Digitalis	Sodium Bismuth Tartrate
Number of patients	10	7	15	7	21
Dose, Gm. or cc.	1.30	1.30	1.3	1.4	2.0
Daily output of urine in control period, cc.	600.00	601.00	742.0	600.0	512.0
Maximum excretion, percentage change	247.00	330.00	1,081.0	263.0	120.0
Total excretion, percentage change	200.00	285.00	685.0	107.0	187.0
Duration of diuresis, days	1.52	0.82	1.3	4.0	4.2
Concentration of chloride in urine, percentage change	+11.2	+26.2	+76.4	—20.3	—11.0
Maximum chloride content of urine, percentage change	+202	+320	+500	+187	+60
Total chloride content of urine, percentage change	+211	+320	+488	+91	+54
Maximum chloride content of blood, percentage change	+1.56	+0.6	+6.6	—11.5	+1.2
Total chloride content of blood, percentage change	+0.23	+1.0	+3.8	—10.2	+0.6

* The maximum percentage change was obtained by averaging the greatest changes observed during diuresis; the total percentage change in the fluid or the chloride content actually removed indicates changes during the entire period of diuresis as compared with the output for an equal control period.

STORAGE OF SODIUM CHLORIDE IN ASCITIC AND EDEMA FLUID

From five of the patients with edema collections of edema fluid were made by means of Southey tubes. Pleural fluid was obtained from two patients with cardiac decompensation and anasarca. Ascitic fluid was obtained after abdominal paracentesis from one patient with cardiac decompensation and from eight patients

10. Loeb, R. F., and others: J. Clin. Investigation **11**:621, 1932.

11. Lashmet, F. H.: The Treatment of Nephritic Edema by Acid, J. A. M. A. **97**:918 (Sept. 26) 1931.

12. Barker, M. H., and O'Hare, J. P.: The Use of Salyrgan in Edema, J. A. M. A. **91**:2060 (Dec. 29) 1928. Barker, M. H., and Kirk, E. J.: Experimental Edema (Nephrosis) in Dogs in Relation to Edema of Renal Origin in Patients, Arch. Int. Med. **45**:319 (March) 1930. Barker.[6]

with portal cirrhosis and ascites. The amount of chloride in these fluids was compared in each case with the concentrations of chloride in the blood and urine. In all but two patients the average concentration of chloride in the edema fluid exceeded that of the blood, and in six patients the chloride content of the edema fluid was even higher than the chloride concentration in the urine. The average sodium chloride content of the blood was 418 mg. per hundred cubic centimeters (with a range from 385 to 469 mg.), while the average concentration in the edema fluid was 618 mg. (with a range of from 357 to 1,200 mg.) and in the urine 671 mg. (with a range of from 360 to 890 mg.).

COMMENT

In order to facilitate discussion and comparison, important numerical data which I have obtained from this and previous studies of the diuretic drugs are summarized in the accompanying table. The drugs are arranged as follows, in ascending order of effectiveness for removing water from the body: bismuth, digitalis, theophylline, merbaphen and salyrgan. Digitalis and bismuth produce a more prolonged diuresis, which is never so dramatic as the sudden outpouring of urine following the administration of a mercurial diuretic. However, there is often a marked diminution in diuresis after the administration of mercurial diuretics which is not observed after the administration of digitalis and bismuth. The total output of sodium chloride in the urine closely parallels the output of urine and is likewise least after the administration of digitalis and greatest after the administration of salyrgan. Digitalis has no direct effect on the kidney and does not act as a diuretic in patients without congestive heart failure and edema.[13] Any renal vasoconstriction due to this drug when given in therapeutic doses is overcome by an increase in the local blood flow, which determines the diuretic effects. Theophylline, merbaphen and salyrgan increase the output of urine even in a normal person. Theophylline aften produces so much gastric irritation that it cannot be tolerated by the patient. No symptoms of mercurial poisoning were observed after the administration of merbaphen and salyrgan to the patients in the present series. One patient received two 2 cc. injections of salyrgan weekly for two years without symptoms of mercurial intoxication.

After the administration of theophylline, merbaphen and salyrgan there is an increase in the chloride content of the blood and a concurrent increase in the concentration of chloride in the urine. Similar results have been observed after the use of theophylline by Curtis[14] and

13. Stockton, A. B.: Am. Heart J. **9**:248, 1933.

14. Curtis, G. M.: The Action of the Specific Diuretics, J. A. M. A. **93**:2016 (Dec. 28) 1929.

Möller,[15] after the use of merbaphen by Lyons [16] and after the administration of salyrgan by Bedford,[17] Crawford and McIntosh,[18] Hatzieganu, Gavrila and Borbil,[19] Nothmann,[20] Hansen, Fosdick and Dragstedt [21] and others. The increase in the chloride content of the blood is in most cases the first to appear, followed in a short time by an increase in the excretion of chloride in the urine. This can be interpreted only as a prior mobilization of chloride from the tissues and suggests some direct tissue action for these diuretic drugs. A similar conclusion was reached by Melville and Stehle [22] and by Nonnenbruch,[23] who observed the same phenomena. Spontaneous diuresis and diuresis produced by digitalis are characterized by a marked decrease in the concentration of chloride in the blood and also by a decrease in the concentration of chloride in the urine. In spite of the decreased concentration of the chloride, however, the daily output of chloride is increased because of the large amounts of fluid excreted. This type of diuresis suggests a simple washing-out effect on free chloride of the tissues which occurs so rapidly that the tissues are unable to maintain the original chloride level of the blood. Consequently, the chloride content falls.

The chlorine ion is notably concerned in the phenomenon of diuresis. According to Herrmann,[24] Melville and Stehle [25] and Frandsen and Möller,[26] an initially low chloride content of the blood forecasts a poor diuretic response to the xanthine diuretic drugs. The sodium ion itself exerts an antidiuretic action, which can be demonstrated easily by the administration of large amounts of sodium chloride. This results in oliguria and an accumulation of fluid in edematous patients, and even the development of frank edema of the ankles in normal persons. Other chlorides, such as potassium chloride, ammonium chloride and hydro-

15. Möller, K. O.: Arch. f. exper. Path. u. Pharmakol. **126**: 143, 1927.

16. Lyons, R.: M. Clin. North America **12**:1341, 1929.

17. Bedford, D. E.: Proc. Roy. Soc. Med. **24**:429, 1931.

18. Crawford, J. H., and McIntosh, J. F.: J. Clin. Investigation **1**:333, 1925.

19. Hatzieganu, I.; Gavrila, I., and Borbil: Compt. rend. Soc. de biol. **99**: 1813, 1928.

20. Nothmann, M.: Arch. f. exper. Path. u. Pharmakol. **172**:402, 1932.

21. Hansen, H. L.; Fosdick, L. S., and Dragstedt, C. A.: J. Pharmacol. & Exper. Therap. **41**:325, 1931.

22. Melville, K. I., and Stehle, R. L.: Arch. f. exper. Path. u. Pharmakol. **123**:175, 1927.

23. Nonnenbruch, W.: München. med. Wchnschr. **68**:1282, 1921.

24. Herrmann, G., and others: Diuresis in Patients with Congestive Heart Failure, J. A. M. A. **99**:1647 (Nov. 12) 1932.

25. Melville, K. I., and Stehle, R. L.: J. Pharmacol. & Exper. Therap. **34**:209, 1928.

26. Frandsen, J., and Möller, K. O.: Acta med. Scandinav. **68**:385, 1928.

chloric acid, cause an increase in the output of urine, rich in chloride, which is proof of the antidiuretic effects of the sodium ion.

Herrmann and his co-workers [27] and Schmitz and Leiter [28] have employed the Rehberg [29] technic in the study of the mechanism of diuretic action. This procedure alone is not acceptable for the purpose, since it has never been demonstrated that creatinine is a nonthreshold substance. In fact, several workers have reported to the contrary.[30] Concurrent increases in the concentration of chloride in the blood and urine and an early prediuretic mobilization of chloride in the blood cannot be explained on the sole basis of decreased tubular reabsorption caused by the diuretic drugs. Moreover, an irritant action of the metallodiuretic drugs on the kidneys could not explain the full effects accompanying diuresis produced by these drugs.

Modern controversies have revolved around the question of the primary seat of action of diuretic drugs, whether it is in the tissues or the kidneys or both. Europeans have generally emphasized the importance of the tissues, while Americans have generally insisted on the importance of the kidneys. Unfortunately, American investigators have not always weighed adequately all the evidence, but when this is done it is difficult to explain satisfactorily the results with some diuretic drugs without giving consideration to a direct action on the tissues. This paper may therefore serve to emphasize the worthiness of this view, certainly, at least, as regards the metallodiuretic drugs. The situation when theophylline is administered appears to be more complicated. My own results with this drug are not as satisfactory as might be desired in support of a tissue action, so that a direct renal action may be the more important factor.

CONCLUSIONS

The metallodiuretic drugs, merbaphen, salyrgan and bismuth sodium tartrate probably act directly on the tissues in general and thus produce a mobilization of chloride and water. This explains adequately the observed facts, namely, the increase in the chloride content of the blood preceding the diuresis and the concurrent increase in concentra-

27. Herrmann, G.; Stone, C. T., and Schwab, E. H.: Some Studies on the Mechanism of Diuresis in Patients with Congestive Heart Failure, J. A. M. A. **98**:2315 (June 25) 1932. Herrmann and others: J. Lab. & Clin. Med. **18**:902, 1933. Herrmann and others.[8]

28. Schmitz, H. L., and Leiter, L.: J. Clin. Investigation **10**:667, 1931. Schmitz, H. L.: ibid. **11**:1075, 1932.

29. Rehberg, P. B.: Biochem. J. **20**:447, 1926.

30. Marshall, E. K., Jr.: Am. J. Physiol. **94**:1, 1930. Jolliffe, N., and Chasis, H.: Proc. Soc. Exper. Biol. & Med. **30**:586, 1933. Shannon, J. A.: ibid. **100**: 301, 1932.

tions of chloride in the blood and urine. A direct renal action of these diuretic drugs cannot fully account for these phenomena.

The xanthine diuretic drugs, notably theophylline, apparently exert a similar direct action on the tissues in part at least, but there is a greater variability in the changes in the chloride content and also in diuresis. The diuretic action appears to be partly of direct renal origin.

Spontaneous diuresis and the diuresis of digitalis in decompensated patients are characterized by increases in the urinary output of chloride and simultaneous decreases in the concentration of chlorides in the urine and blood, thus indicating a fundamental difference in the mechanism of diuresis produced by metallodiuretic drugs. Here an improvement of the renal circulation appears to be paramount.

Clinical results in edematous patients indicate the following arrangement of drugs in the ascending order of their diuretic efficiency: bismuth, digitalis, theophylline, merbaphen and salyrgan.

Progress in Internal Medicine

SYPHILIS

A REVIEW OF THE RECENT LITERATURE

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The present review is similar in every respect to that of a year ago [1] and covers the publications which appeared during the last six months of 1935 and the first six months of 1936. The shorter span of time to be covered has made it possible, in a few instances, to be more detailed, but the limitations of space have again made it necessary to exercise a rigid and sometimes rather arbitrary selection of material. In the field of experimental syphilis, only those articles which are of general interest or which have a direct clinical application have been mentioned, and, aside from one contribution of crucial importance, references to the welter of literature on the serology of syphilis have been almost entirely omitted. The preponderance of the American literature reviewed was not planned; it occurred automatically as a reflection of the heightening of interest in syphilis which is taking place in this country.

HISTORY OF SYPHILIS

The valuable contributions of Zimmermann,[2] Klauder,[3] Krumbhaar,[4] Beekman [5] and many others do not lend themselves well to review but should be mentioned here. Further studies in paleopathology by Williams [6] and Henschen,[7] however, are of great interest in serving

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1. Moore, J. E.: Syphilis: Review of the Recent Literature, Arch. Int. Med. **56**:1015 (Nov.) 1935.

2. Zimmermann, E. L.: The Early History of Alopecia Syphilitica, Janus **39**:105 (June-Aug.) 1935.

3. Klauder, J. V.: Syphilis and the Characters in Ibsen's Dramas, Ann. M. Hist. **8**:236 (May) 1936.

4. Krumbhaar, E. B.: Pre-Columbian Peruvian Tibia, Ann. M. Hist. **8**:232 (May) 1936.

5. Beekman, F.: Studies in Aneurysm by William and John Hunter, Ann. M. Hist. **8**:124 (March) 1936.

6. Williams, H. U.: The Origin of Syphilis: Evidence from Diseased Bones, Arch. Dermat. & Syph. **33**:783 (May) 1936.

7. Henschen, F.: The Earliest History of Syphilis in Light of More Recent Skeleton Findings, Hygiea **97**:592 (Aug. 31) 1935.

further to clarify the question of the origin of syphilis in America. To his former reports Williams adds information on three additional groups of bones (from Mexico, Alabama and Illinois) which are unquestionably of precolumbian origin and which are diseased in the manner characteristic of syphilis. Complementary to this, Henschen has reviewed the material of the European museums and reports that, whereas in the anatomic material dated prior to the first portion of the sixteenth century there are to be found no examples of disease of bones like that caused by syphilis, after about 1550 such examples occur in abundance.

SPIROCHAETA PALLIDA

The controversy concerning the existence of an invisible form of Spirochaeta pallida proceeds with undiminished vigor with, at the moment, the protagonists on the offensive. Nyka,[8] unable to see convincing examples of multiplication of the spiral form of the organism when observing preparations for long periods under the dark field microscope, concludes that reproduction must take place while the organism is in a filamentous stage. With the collaboration of the staffs of the Pasteur and the Alfred Fournier Institute, Levaditi[9] in two long general articles produces the following evidence in favor of an infravisible form of S. pallida: 1. S. pallida may be found in sections stained by the Dieterlé method (and less easily by dark field examination) of tissues from infected mice, but if heat-killed instead of live organisms are injected into an animal in a similar manner they are not found in sections of remote tissues. This is interpreted as meaning that the organisms in the tissues are developed locally from invisible forms. 2. Tissue from infected animals will produce syphilis in other animals even when no spiral forms of the organism are found in sections or dark field preparations. 3. An initial pause, or prespirochete phase, occurs after an animal is inoculated with an emulsion of virulent spirochetes. 4. The difficulties of producing involvement of the central nervous system in experimental animals and the characteristics of human neurosyphilis are adduced to explain the assumption that only the infravisible form of the spirochete may survive in the tissue of the nervous system.

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8. Nyka, W.: A propos de la multiplication du spirochète syphilitique, Compt. rend. Soc. de biol. **121**:97, 1936.

9. (*a*) Levaditi, C.; Vaisman, A.; Schoen, R., and Manin, Y.: Recherches expérimentales sur la syphilis (deuxième mémoire): Variations de l'activité pathogène et cycle evolutif du virus syphilitique, Ann. Inst. Pasteur **56**:251 (March) 1936. (*b*) Levaditi, C.; Vaisman, A., and Schoen, R.: Recherches expérimentales sur la syphilis: Étude pathogénique de la neurosyphilis, ibid. **56**: 481 (May) 1936.

Koch,[10] on the other hand, critically examined the subject and concludes that there is no direct evidence for the existence of an infravisible form of S. pallida and further that there are no observed phenomena which necessitate for their explanation the hypothecation of an infravisible form of the organism. By appropriate experiments he demonstrated that there is no filtrable form of the organism, a point clearly demonstrated by Castellino [11] also. In following a group of animals through the "initial pause" he observed that the argentophilic granules, which Levaditi and his co-workers consider to be another form in the life cycle of the spirochete, could be seen in sections only *after* typical spiral forms were present in abundance. He concludes, therefore, that the granules, if related to the spiral form at all, represent degeneration products.

A Spirochete Vaccine.—Levaditi and his collaborators [9a] have carried the Truffi strain of S. pallida in their laboratory since 1908. Inoculations of human beings in 1914, 1922 and 1935 produced progressively less typical infections, and in 1935 the strain failed entirely to infect a chimpanzee in which typical syphilitic lesions developed when a freshly isolated strain was injected. From this experience they suggest that eventually it may be possible to develop an attenuated organism suitable for use in the vaccination of human beings.

The Viability of S. Pallida in Excised Tissue.—Pathologists have long wondered to what risks they were exposing themselves in handling tissues from syphilitic patients. Rosahn [12] suggests the answer. Rabbit syphilomas rich in spirochetes were removed and stored at ordinary refrigerator temperature. At intervals varying from twenty-four hours to forty-two days, portions of a syphiloma were ground up and inoculated intratesticularly into rabbits in the usual manner. Infection resulted after the injection of material stored for seven days or less but not after that stored for from fourteen to forty-two days.

GENERAL LABORATORY PROCEDURES

The Staining of S. Pallida.—In a brief communication Krajian [13] describes in duplicatable detail a method for staining S. pallida in tissue, which can be carried out from fresh tissue to stained and mounted

10. Koch, F.: Ueber Mutation der Spirochaeta pallida, Arch. f. Dermat. u. Syph. **172**:51, 1935.

11. Castellino, P. G.: Gior. ital. di dermat. e sif. **77**:91 (Feb.) 1936.

12. Rosahn, P. D.: The Infectivity of Treponema Pallidum in Excised Syphilitic Tissue, Am. J. Hyg. **22**:283 (Sept.) 1935.

13. Krajian, A. A.: A Rapid Method of Staining Spirochaeta Pallida in Single Sections of Tissue, Arch. Dermat. & Syph. **32**:764 (Nov.) 1935.

section in an hour and a half. He states that the organisms are easy to find in primary lesions and makes the interesting suggestion that in a central laboratory the diagnosis of early syphilis by means of sections of biopsy material from a suspicious lesion that are stained in this manner may be more reliable than diagnosis by dark field examination of tissue juice which has been transported from a distance. The method has not as yet been sufficiently used to establish its value in detecting the organisms in lesions of late syphilis, which make up the vast majority of necropsy material.

The Sedimentation Rate in Syphilis.—Gaté and Chevat [14] report studies of the sedimentation rate before and during treatment of 70 patients with various forms of syphilis. Using the method of Cordier, they found the sedimentation rate to be increased by from 8 to 20 per cent in patients with seropositive primary syphilis, and in the group with secondary syphilis it reached as high as 55 per cent. On the institution of treatment the sedimentation rate was observed in some instances to increase, suggesting a provocative response, but in all it soon fell to a level around 15 per cent, there to remain until about the end of the first year of treatment, irrespective of the results of the serologic test for syphilis. There was no uniformity among patients with late or congenital syphilis, but the behavior of the sedimentation rate closely paralleled the clinical course. The authors suggest that from an extension of these observations might be developed a guide for the treatment of early syphilis after seronegativity has been attained.

SEROLOGY

Various reports [15] have been given of the meeting of the committee on Evaluation of Serodiagnostic Tests for Syphilis. The following quotation is from an editorial [16] entitled "The American Evaluation of Serodiagnostic Tests for Syphilis from the Clinician's Standpoint:"

> The report of the meeting of the Committee on Evaluation of Serodiagnostic Tests for Syphilis in the United States, recently held under the auspices of the

14. Gaté, J., and Chevat, H.: Contribution a l'étude de la sédimentation des Hématies dans la syphilis, Presse méd. **44**:71 (Jan. 11) 1936.

15. Cumming, H. S.; Hazen, H. H.; Sanford, F. E.; Simpson, Walter M., and Vonderlehr, R. A.: The Evaluation of Serodiagnostic Tests for Syphilis in the United States: Report of Results, Ven. Dis. Inform. **16**:189 (June) 1935. Senear, F. E.; Cumming, H. S.; Hazen, H. H.; Sanford, A. H.; Simpson, W. M., and Vonderlehr, R. A.: Evaluation of Serodiagnostic Tests for Syphilis, South. M. J. **29**:68 (Jan.) 1936. The last mentioned article gives a summary of the report.

16. The American Evaluation of Serodiagnostic Tests for Syphilis from the Clinician's Standpoint, editorial, Am. J. Syph., Gonor. & Ven. Dis. **20**:207 (March) 1936..

United States Public Health Service and the American Society of Clinical Pathologists, is not entirely satisfactory from the standpoint of the clinician. In rating tests as to sensitivity and specificity, doubtful results in both syphilitic and nonsyphilitic patients were excluded from consideration since "there was no general agreement in the proposals offered by the participating serologists for the evaluation of this group of reports." Specificity (as to blood, not spinal fluid, tests—this editorial comment being limited to the results with blood specimens only) was determined by the results in 152 normal nonsyphilitic individuals only, no consideration being given in the widely publicized preliminary reports to the 316 presumably nonsyphilitic patients with diseases and conditions other than syphilis (i. e., tuberculosis, neoplasms, jaundice, fevers, pregnancy, menstruation, etc., but excluding the groups of patients with malaria and leprosy). This limitation, corrected in the final report, was deliberate since the 152 normal subjects were considered to be clinically beyond suspicion of infection with syphilis, while it was felt that in spite of every clinical precaution a very small percentage of the 316 presumably nonsyphilitic patients with various conditions might in fact have had syphilis. Finally, the Committee was scrupulously careful to avoid specific recommendations for the adoption of any particular test or group of tests.

Before proceeding to a discussion of these points, it is necessary to point out that the competitive tests were carried out by thirteen serologists, each of whom performed in his own laboratory the test which he himself had devised (exceptions only in the cases of Kurtz, who performed the Kahn presumptive test, and Rein, who performed the Kline exclusion test). In all instances, therefore, the results may be taken to indicate the maximum efficiency of the various tests under the conditions imposed, since the originator of the test may be expected to be more familiar with the major and minor details of his own procedure than technicians in other laboratories. However, the criterion by which any laboratory procedure may be expected to stand or fall is its efficiency in other hands than those of its originator. For this reason, a projected serologic evaluation plan has been properly sponsored by the same agencies responsible for the first and is now under way. In this second project, specimens are being sent to each of several laboratories, as well as to that of the originator of the test, performing, for example, the Kahn or Kline flocculation tests, the Ruediger complement fixation test, etc. The results of this second evaluation will be a much better indicator of the efficiency of the several tests under everyday working conditions in the average serologic laboratory, and the decision as to the relative merits of each properly should be deferred until its conclusion.

The purpose of these comments is, however, to discuss the interpretation of the published results of the original serologic evaluation study from the standpoint of the clinician, whether or not he possesses practical experience in the serologic laboratory. It should be unnecessary to reemphasize, though apparently further emphasis is still desirable, several important points in connection with the clinical interpretation of serologic tests for syphilis, viz:

1. The clinician desires that the laboratory shall employ a test which is positive in the highest possible percentage of patients infected with syphilis (i. e., of maximum sensitivity) but which is uniformly negative in nonsyphilitic individuals (i. e., of maximum specificity).

2. The several complement fixation (Wassermann) and flocculation tests for syphilis depend on identical physicochemical phenomena and differ from each other only in certain technical details. The flocculation tests, requiring only one ingredient (antigen) in addition to the patient's serum, are simpler to perform than

the complement fixation tests (which require antigen, complement, amboceptor, and sheep or human red cells in addition to patient's serum); but this simplicity of performance is in part counterbalanced by greater difficulty of interpretation, especially in the hands of relatively unskilled technicians.

3. No test yet devised is so sensitive as to be uniformly successful in detecting the presence of syphilis or so specific as to avoid an occasional false positive result in a nonsyphilitic person.

4. Variations in sensitivity and specificity both may be produced by variations, often minor, in the reagents employed in the test or the physical conditions under which it is performed. In general, however, sensitivity is increased at the expense of specificity, and vice versa: i. e., it is technically possible to perform a test so sensitive as to be positive on all serums submitted, even those from normal persons, or one so insensitive as to be negative on all serums, even those from patients with secondary syphilis. The best available present-day test should be that which compromises with these technical factors to provide the largest possible number of positive tests in syphilitic patients and the smallest number of positive tests in nonsyphilitic individuals.

5. The current custom of reporting the results of serologic tests in terms of plus marks (i. e., 4 + denoting strongly positive; 3, 2, 1 plus or plus-minus denoting varying degrees of weakly or partially positive, or doubtful; and 0 equaling negative) is inaccurate and misleading. "Four-plus" does not necessarily mean "strongly positive" since all tests in current use are qualitative or only roughly quantitative: that is, they are performed with a fixed amount of whole serum related to the total bulk of the test and ranging from 0.1 to 0.025 cc. Actually, a test may be positive with as little as 0.00005 cc. of whole serum. In such a case, if plus marks are to be used in reporting, the result might properly be expressed as "four-thousand-plus" instead of "four-plus." The current terminology of "four-plus" covers a range of positivity extending from 0.1 to 0.00005 cc. (or even less). Under these circumstances, it is obvious that plus marks, and the qualifying adjective "strongly," should be eliminated from routine serologic terminology and should be replaced by the single word "positive."

Though "positive" covers an extreme range of variation in terms of the amount of patient's serum employed in the test, the other symbols (+ + +, + +, +, ±, i. e., 3, 2, 1 plus, etc.), commonly used to describe a "partially positive" or "doubtful" result, cover instead an extremely minute range of variation. With the Wassermann test, for example, and with the usual total volume of 1.0 to 1.25 cc., this range is only between the limits of 0.2 and 0.02 cc. of whole serum. Within this narrow range, there is no valid excuse for the attempt to report minute variations in the degree of positiveness, and all such results should be expressed by the word "doubtful."

6. Aside from syphilis, the only disease conditions which give positive results with serologic tests for syphilis are yaws, relapsing fever, leprosy (all frequently), and malaria (infrequently). With rare exceptions, positive tests in all other nonsyphilitic individuals are due to technical error (common mistakes which are to be guarded against by repetition and intra- or interlaboratory check) or to biologic phenomena (very rare, and too intricate for discussion here).

7. Doubtful serologic tests may be due to syphilis (e. g., as a stage in the appearance of reagin—the name given to the substance producing a positive test—early in the disease, or in its disappearance later, either spontaneously or more often under the influence of treatment, at both of which times but a very small

amount of reagin may be present). In nonsyphilitic individuals, doubtful results may be due to technical error, to faulty interpretation, to attempts to increase the sensitivity of a given test beyond its particular limits of safety (all common errors), or to the same biologic phenomena which rarely cause a false positive result.

8. In the absence of the disease conditions enumerated in paragraph 6, *a positive serologic result properly controlled for technical and biologic error means that the patient has syphilis.*

9. Since no test is as yet so sensitive as to detect all instances of syphilitic infection, *a negative result does not exclude the presence of syphilis.*

10. A doubtful result may mean that the patient has syphilis. Since this is so, such a result obtained in a nonsyphilitic individual is often as confusing to the clinician as a false positive report.

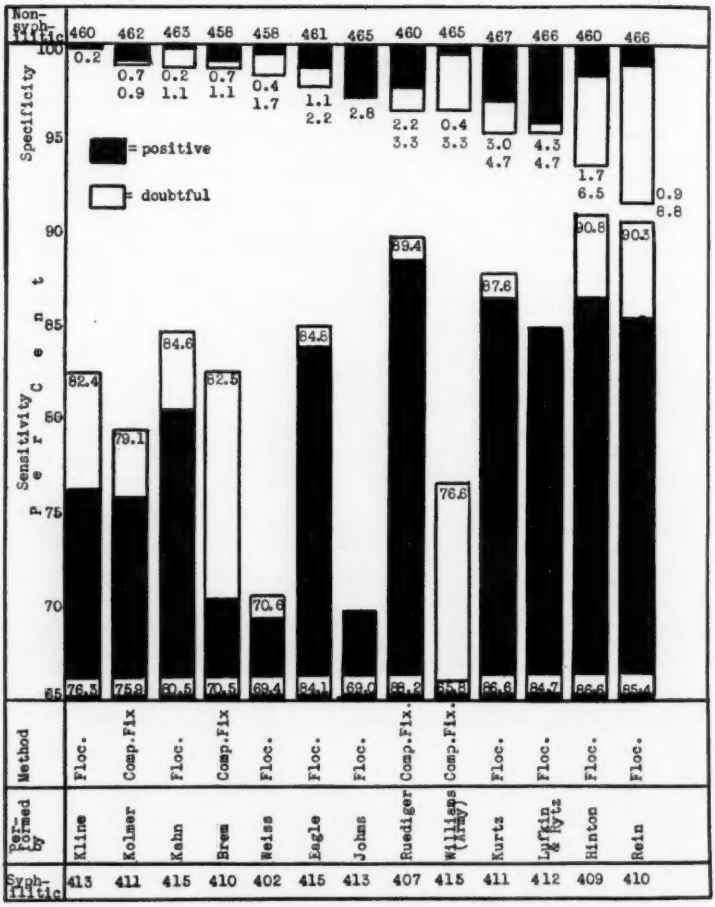
11. The proper person to interpret serologic results is not the serologist, who usually has no contact with the patient, but the clinician, who can fit the laboratory data with history and physical findings. Manifestly, the clinician will be better fitted to accomplish this task if he is familiar, not necessarily with the technical details of performing serologic tests, but with the accomplishments and limitations of the test which he is employing.

This lengthy introduction is a necessary preliminary to a reconsideration of the results of the American plan for serologic evaluation. In this reconsideration and in view of the preceding discussion, the results obtained by the competing serologists have been rearranged to show (1) sensitivity, the percentage of positive *and* doubtful results obtained in the 415 blood specimens from syphilitic patients; and (2) specificity, the percentage of positive *and* doubtful results obtained in the 152 normal nonsyphilitic persons *plus* the 316 persumably nonsyphilitic individuals with other diseases or conditions. The increased number of nonsyphilitic serums provides a much more accurate basis of evaluation of specificity.

Though it is obvious that a doubtful result in a known syphilitic patient is not as convincing as a positive result, it is nevertheless scorable as a partial success for the competing serologist. Conversely, while a false doubtful result in a nonsyphilitic individual is not as disturbing to the clinician as a false positive test, it is nevertheless disturbing enough and as such scorable as a partial failure for the serologic plan in question.

To the clinician interested primarily in diagnosis, specificity is a more important factor than sensitivity. It is particularly desirable to employ as a routine diagnostic test one which provides the smallest possible number of nonspecific reactions (whether positive or doubtful) in nonsyphilitic persons. A diagnosis of syphilis made in an uninfected individual is a disaster of the first magnitude. If maximum specificity demands some sacrifice of sensitivity, the clinician is quite willing to accept the sacrifice.

Figure 1, therefore, ranks the participating serologists in order of specificity, reading from left to right. The sensitivity of each test is also shown in the same figure, in order to permit ready comparisons. If one utilizes as a satisfactory standard of specificity that chosen by the serologists (both of the American and the Montevideo Conference), i. e., less than 1 per cent false positive tests in nonsyphilitic persons, seven tests qualify as satisfactory. If, however, false doubtful results are added to the false positives, only four are satisfactory: Kline diagnostic, Kolmer complement fixation, Kahn diagnostic, and Brem complement fixation. If the second American evaluation study confirms the first, one or more of these four tests should be adopted for routine diagnostic use. Of the four, the two most sensitive are the Kahn and Kline flocculation tests.



This chart is an adaptation and rearrangement of the chart provided in the final report of the Committee on Evaluation of Serodiagnostic Tests for Syphilis in the United States. The percentage scale has purposely been arranged to run from 65 to 100 per cent, rather than from 0 to 100 per cent, in order to magnify the differences in the results of the competing serologists. The figures below the blocks denoting sensitivity show for each test (the upper number) the incidence of false positive results and (the lower number) the total incidence of false positive plus false doubtful results. The figures within the lower black blocks indicate the percentage of positive results obtained for syphilitic patients; the figures within the lower white blocks show the percentage of positive plus doubtful tests obtained for syphilitic patients. In the lines at the top and bottom of the page labeled nonsyphilitic and syphilitic, the numbers signify the actual number of specimens examined by each serologist. Note that all tests except four were successful in obtaining 80 per cent or more of positive plus doubtful tests in patients with known syphilis and that, in general, there is a tendency for a decrease of specificity corresponding with an increase of sensitivity. For diagnostic purposes the first four tests to the left of the chart are probably preferable; for the increased sensitivity demanded for the special purposes enumerated in the text, the Ruediger complement fixation test and the Hinton and Kline exclusion flocculation tests (Rein) are the methods of choice. (Reproduced from the *American Journal of Syphilis, Gonorrhea and Venereal Diseases* **[20**:212, 1936].)

Six serologists—Ruediger (complement fixation), and Eagle, Kurtz (Kahn presumptive), Lufkin and Rytz, Hinton, and Rein (Kline exclusion), all of these five latter flocculation tests—have tests of slightly higher sensitivity than the Kline or Kahn diagnostic tests. In each instance, however, this increased sensitivity is achieved at the cost of loss of specificity. Kline and Kahn have recognized this fact in the naming of their more sensitive tests ("presumptive" and "exclusion" tests); but too many clinicians do not realize the inference of these special names. If these results are confirmed by the second American evaluation study, it would be desirable to limit the use of these more sensitive but less specific serologic tests to three sets of circumstances: (1) in the serologic testing of donors for blood transfusion, as an added safeguard for the prevention of transfusion syphilis; (2) as serving special syphilis clinics, where the results are susceptible of expert clinical interpretation; or (3) in following the results of treatment in patients definitely proved to have syphilis. In the absence of such limitations, the clinician served by a laboratory which employs one of them as a routine diagnostic measure must be prepared to accept a risk, ranging from 2 to nearly 9 per cent, of false nonspecific results in nonsyphilitic patients.

Wilson and Levin[17] confirm the fact that malaria may produce false positive results of serologic tests for syphilis. From 1930 to 1934 these authors observed 262 patients with proved malaria, for each of whom were made a Kolmer complement fixation test and either a standard Kahn or a diagnostic Kline flocculation test. On the basis of the history, previous and subsequent serologic tests and physical examination it was decided that 23 of the 70 who manifested positive results certainly, and that an additional 23 probably, had syphilis. For 9 of the remainder the information was inadequate, but 15 (6.3 per cent of the nonsyphilitic patients) who manifested positive serologic results (there was little agreement between the complement fixation and the flocculation tests, however) were later shown by careful study and follow-up not to have syphilis. In one of these a positive result of a cerebrospinal fluid test was obtained during malaria; the result was later normal. In 7 others of these 15 patients the cerebrospinal fluid was normal.

The Relationship Between Serologic Tests of the Blood and Those of the Cerebrospinal Fluid.—Unfortunately the Serologic Conference did not specifically consider this point, but in their 307 patients with late syphilis who had had varying amounts of treatment, the highest percentage of positive results of serologic tests was 86.4 (Ruediger, complement fixation), and the tests with higher specificity fell well below this figure. In the light of the incidence of neurosyphilis one does not need the report of Grund,[18] of 5 patients with a negative result of the

17. Wilson, R. J., and Levin, S. L.: Observations on Effect of Malaria on Wassermann Reaction, Am. J. M. Sc. **191**:696 (May) 1936.

18. Grund, J. L.: The Exclusion of Neurosyphilis by Means of the Hinton Reaction of the Blood, Arch. Dermat. & Syph. **32**:569 (Oct.) 1935.

Hinton type of flocculation test of the blood but a positive result of tests of the cerebrospinal fluid, to conclude that a negative result of a test of the blood serum does not exclude the possibility of involvement of the neuraxis.

THE SOCIAL AND PUBLIC HEALTH ASPECTS OF SYPHILIS

Dissemination of Information.—Since the shut-down of the venereal disease control program, which operated effectively both here and abroad during the World War, physicians interested in the control of syphilis have labored against almost insurmountable difficulties. The profession was apathetic, and public ignorance could not be combated because the press forbade the use of the word syphilis or any of its implications.

In the past quintade, however, the profession has been so barraged by the studies of the Cooperative Clinical Group and other contributions derived therefrom or based on similar lines that, in Nelson's [19] opinion:

> The diagnosis and management of syphilis, and especially of early syphilis, have been written and talked about so much in recent years that there is bound to be trouble ahead for the physician who makes mistakes in diagnosis or who fails to treat the patient properly. Appearance before the Board of Registration in Medicine is the least that can happen. Suits for malpractice will follow as rapidly as the public becomes acquainted with what it has a right to expect from the physician.

Ideally, of course, Nelson is right; practically, he fails to recognize that the apathy of many physicians in regard to syphilis arises from their lack of fundamental training. Clarke and Exner [20] supplement Exner's [21] earlier study on the teaching of syphilology in medical schools by a statistical study of hospital practice in the training of interns. Of 331 hospitals with outpatient departments which responded to inquiry, 243 required service of some or all interns in the clinic for syphilitic patients; in an additional 70 such service was optional, but there were 17 hospitals which did not make the service for syphilitic patients available to their interns! Also, the tour of duty in the hospitals in which this service was required was found to vary widely, with extremes of six and seven hundred and twenty hours of attendance, showing an average of fifty-eight hours distributed over a period of ten weeks. In those hospitals in which service in the clinic for syphilitic patients was

19. Nelson, N. A.: Correspondence Entitled "Trouble Ahead," New England J. Med. **213**:941 (Nov. 7) 1935.

20. Clarke, C. W., and Exner, M. J.: The Training of Interns in Syphilology, J. A. M. A. **106**:767 (March 7) 1936.

21. Exner, M. J.: Report on Instruction Regarding Syphilis in American Medical Schools, Am. J. Syph. **17**:449 (Oct.) 1933.

optional, the average period of service was somewhat less, and not all hospitals reported that the interns worked under competent supervision.

It has long been obvious, however, that granted an adequate level of professional competence, the control of syphilis must necessarily depend largely on dissemination of information to the laity, which has in the past been practically impossible because of the attitude of the press. In the recent past, however, enlightened editors in many of the larger cities have published feature articles and important news items regarding syphilis, and Parran,[22] in a careful summary of the important facts, with a wise avoidance of theatrical effects, reached probably a majority of the reading public.

Results.—Nelson [23] shows that a determined effort to control syphilis actually accomplishes its aim. Contrasting the situation in Massachusetts for the period 1915 to 1919 with that for 1934, he found a 70 per cent reduction in the number of cases of syphilis among pregnant women, a 30 per cent reduction in the number of patients admitted to clinics for syphilitic treatment and in reports of cases of early syphilis from physicians and hospitals and a 32 per cent reduction in the number of cases of neurosyphilis reported. The incidence of gonorrhea during the same period did not decline.

The Cost of Syphilis.—Thompson, Brumfield and Caldwell [24] carefully studied conditions in Baltimore and determined that for the year 1933 the direct cost of syphilis to that representative community of 828,000 persons was $170,000. This does not include any of the indirect costs, which are listed but which could not be determined and were not estimated. Forty-five per cent of this sum was contributed by privately endowed charity. The significant finding was, however, that the bulk of the funds was being expended in the treatment or institutional care of patients with late syphilis, largely with irremediable cardiovascular disease and neurosyphilis; and these authors emphasize that a relatively modest increase in the sums expended for the treatment of early syphilis would soon pay handsome dividends in reducing this load of caring for patients with late syphilis.

Methods for the Control of Syphilis.—Syphilis has become a rare disease in the Scandinavian countries and is decreasing in extent in Great Britain. In the course of developing adequate facilities for the

22. Parran, T., Jr.: The Next Great Plague to Go, Survey Graphic **25**:405 (July) 1936. Why Don't We Stamp Out Syphilis? Reader's Digest **29**:65 (July) 1936.

23. Nelson, N. A.: The Decreasing Prevalence of Syphilis in Massachusetts, J. A. M. A. **106**: 105 (Jan. 11) 1936.

24. Thompson, W. C.; Brumfield, W. A., and Caldwell. L.: The Direct Cost of Syphilis in a Representative American City, Am. J. Syph., Gonor. & Ven. Dis. **20**:243 (May) 1936.

control of syphilis in the city of New York, a committee, headed by Dr. John L. Rice, the Commissioner of Health, during the summer of 1935 visited Scandinavia and Great Britain to investigate the methods used there. The general conclusions stated in the detailed report [25] were as follows:

In each of the countries studied by the Commission, there appears to have been a downward trend in the prevalence of syphilis since the peak in 1919 or 1920. The prevalence of gonorrhea has shown less change and may be said to have remained comparatively unaffected by the measures which have been taken in the several countries.

Several causes are believed to have played an important part in the decrease of syphilis. First and most important are believed to be the basic scientific fact that treatment renders syphilis noninfectious and the fact that in all of these countries diagnosis and treatments are free, accessible, and generally good. At the beginning of the downward trend, when the descent was sharpest, natural causes played an important part. The epidemic had spent its force. Vigorous health propaganda also led infected persons to seek treatment and so to become noninfectious, and warned uninfected people to avoid infection. It is impossible to allocate to these various factors their appropriate ratio of credit for the reduction of syphilis, but it is generally believed in Great Britain and the Scandinavian countries that prompt and adequate treatment of infectious cases was most important.

In Sweden and Denmark diagnosis and treatment are provided at the expense of the state. In Great Britain they are at the expense of the state and the local governmental units. In Norway, for the most part, they are provided as a feature of the health insurance scheme. In all countries diagnosis and treatment are free to all without economic distinction.

In Sweden, Norway, and Denmark an important feature for the plan of combating syphilis and gonorrhea is ample facilities for hospitalization. A large proportion of infectious cases in these countries is hospitalized. In Great Britain proportionately fewer cases are given hospital care.

Public health measures for the control of syphilis and gonorrhea in all the Scandinavian countries are based on the principle that these diseases are communicable and should be dealt with as such. The law requires the reporting of cases, obligates patients to receive treatment, gives health authorities the power to enforce medical care including hospitalization if necessary, penalizes the knowing transmission of infection, and authorizes the finding and the bringing under control of all sources of infection and of all delinquent patients. While persuasion is usually successful, coercive measures are provided for that very small proportion of patients who are uncooperative. In Great Britain, on the other hand, syphilis and gonorrhea are not reportable and not quarantinable; treatment is entirely voluntary, and the health authorities have no power to intervene for the protection of the public health even with the most infectious and uncooperative cases.

If a comparison is made briefly between the Scandinavian countries and Great Britain on the one hand, and the United States on the other, it is seen that our

25. Clarke, C. W.: Control of Syphilis and Gonorrhea in the Scandinavian Countries and Great Britain: A Report of the New York City Commission to Investigate the Prevention and Control of Syphilis and Gonorrhea in Scandinavian Countries and in Great Britain, Am. J. Syph., Gonor. & Ven. Dis. **20**:1 (July, pt. 2) 1936.

policy and practices more nearly resemble those of the Scandinavian countries, for we have all the legal powers of those countries to deal with syphilis and gonorrhea as communicable diseases. Unlike the Scandinavian countries and Great Britain, there are not in the United States free and accessible facilities for the diagnosis and treatment of syphilis and gonorrhea regardless of economic status. The critical problem in America may be said to be that of overcoming these obstacles and bringing all infectious cases of syphilis and gonorrhea, regardless of economic status, under medical care.

Rietz,[26] who is Commissioner of Health in Stockholm, reports in detail the mechanism of the control of venereal disease in Sweden. The backbone of the program is a law, passed in 1918, which contains the following specific points:

1. Every person suffering from venereal disease must submit to treatment by a physician and must follow his directions.

2. Every such person has the right, irrespective of the size of his income, to obtain free medical treatment and medicine, in case he is not being treated by a private physician. This includes free injections, free serologic examinations, as well as free certificates required by the public health authorities as to complete recovery or continued treatment. Hospitalization in a special general ward is also furnished free of charge.

3. Every physician treating a new case of venereal disease must try to obtain information about the source of infection.

4. Against patients who do not properly follow up their treatment and against individuals identified as the source of infection but unwilling to come to treatment certain compulsory measures may be taken.

5. A person who knows that he or she suffers from venereal disease and who by carelessness causes its transmission is subject to punishment of a severity up to forced labor.

6. Every marriage partner prior to obtaining a marriage license has to sign a statement certifying his or her freedom from venereal disease in a contagious stage.

7. The local public health authorities must publish information about the existence of the clinics for the treatment of venereal diseases.

Added to this has been the most determined search for every source of infection until now, from a peak of 44 new cases of syphilis per year per ten thousand population, the rate has dropped to less than 2 per ten thousand in Stockholm. The disease has virtually disappeared in the rural districts.

A committee of experts, cooperating with the United States Public Health Service, has recently drawn up a series of recommendations for a program for the control of venereal disease.[27] They recommend that

26. Rietz, E.: The Prevention of Venereal Disease in Sweden, Am. J. Pub. Health **26:** 357 (April) 1936.

27. Vonderlehr, R. A., and others: Recommendations for a Venereal Disease Control Program in State and Local Health Departments, Ven. Dis. Inform. **17:**1 (Jan.) 1936; J. A. M. A. **106:**115 (Jan. 11) 1936.

from the administrative side such a program should be under the full time direction of an officer for the control of venereal disease but should be closely coordinated with the division for communicable diseases, of the health department and with members of the medical profession and social service agencies and that the allocation of funds for the control of venereal disease be in proportion to the magnitude of the problem in the given locality. Facilities for treatment must be provided which are adequate to provide diagnosis and emergency treatment of any patient who applies, to care for any patient referred by a physician either for treatment or for consultative advice and to provide treatment for all who cannot afford to pay. In large centers the subsidy of existing large clinics rather than the establishment of new isolated units is advised, and the details of how best to accomplish these desiderata in rural communities are given.

The committee emphasizes the necessity of a routine serologic test for syphilis in pregnancy, preferably more than once, points out the desirability of epidemiological work both in the finding of contacts and in the tracing of patients who have lapsed and stresses the necessity for adequate laboratory facilities for diagnosis and treatment. An informative educational program, both for the laity and for the profession, is advised, and finally the results of such a program should be checked, both by accurate mortality and morbidity data and by more elaborate statistical surveys.

Parran [28] indicates that such a program has largely been placed in effect in the state of New York, and Massey [29] indicates that portions of such a program are applicable to a rural county of Maryland in which syphilis is prevalent. Reinhard and Fales [30] describe the technic of follow-up used by the health department in Baltimore and show that efforts to follow the delinquent and persuade (or occasionally force) the recalcitrant patients are far from fruitless.

As a rule, the American authorities favor avoidance of compulsion, such as the Ontario regulations [31] include, preferring education and persuasion as probably slower but more certain methods of accomplishing the eventual eradication of syphilis. There are many who have had a large experience with persons in the lower strata of society, however,

28. Parran, T., Jr.: Syphilis Control in New York State, Ven. Dis. Inform. **16**:303 (Sept.) 1935.

29. Massey, B.: Twelve Months' Syphilis Control Effect in a Rural County, Ven. Dis. Inform. **17**:151 (June) 1936.

30. Reinhard, F. O., and Fales, W. T.: Delinquent Patients in Venereal Disease Clinics, J. A. M. A. **106**:1377 (April 18) 1936.

31. Pequegnat, L. A.: The Applied Aspects of the Venereal Disease Legislation of Ontario, Canad. Pub. Health J. **27**:228 (May) 1936.

who, viewing Sweden's record in the control of syphilis with envy, listen sympathetically to Rietz [26] when he says:

> Though personal liberty is safeguarded in Sweden at least as carefully as in America, the law imposes a very definite restriction of freedom upon persons afflicted with venereal disease, compelling them to accept an amount of medical treatment, not according to their own choice, but according to the decision of responsible physicians. Upon individuals, under such control and to whom complete medical facilities for treatment are available at no cost, the nation further imposes the responsibility not to propagate the disease. For willful neglect of this responsibility, punishment up to the severity of forced labor can be imposed.

Finally, Vonderlehr [32] reemphasizes that the crux of the control of syphilis is the adequate treatment of early syphilis; by no other known means may the incidence of syphilis be materially reduced. With the adequate treatment (which necessitates early diagnosis) of early syphilis, it would be possible in a short generation to duplicate the Scandinavian record.

DRUGS

The Investigation of New Drugs Designed for the Treatment of Syphilis.—Snodgrass [33] clearly restates the conditions which must be fulfilled before any judgment may be rendered as to the applicability of a new drug to the treatment of syphilis in human beings:

1. An ample supply of the drug must be furnished the investigator, and unlimited time must be allowed for the investigation.
2. All details of chemical composition and chemical stability must be known.
3. The technic of administration, i. e., the route, special solvents required and unusual methods to be employed, should have been worked out by the manufacturer.
4. Then, by means of animal experimentation:
   (*a*) The lethal dose unit of drug per animal weight and mode of death must be determined.
   (*b*) The toxic manifestations, early and late, of a sublethal dose should be determined.
   (*c*) Histopathologic studies of the organs of animals killed by the drug and of animals given sublethal doses should be made to determine masked effects on important organs.

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32. Vonderlehr, R. A.: The Control of Syphilis with Special Emphasis on Adequate Treatment as a Control Measure, Ven. Dis. Inform. **16**:413 (Dec.) 1935.

33. Snodgrass, W. R.: Methods to Be Employed in the Investigation of New Substances Designed for the Treatment of Syphilis, Brit. J. Dermat. **48**:11 (Jan.) 1936.

(*d*) Efforts should be made to determine the cause of reactions, and means should be sought to prevent or to treat them.

(*e*) The therapeutic index, i. e., the minimum lethal dose/ the minimum curative dose, should be determined for rabbits with syphilis.

(*f*) The incidence of relapse in rabbits with syphilis after treatment should be noted.

5. If the results of animal experiments are favorable, clinical trial on human beings with syphilis is justified if appropriate safeguards to the patient and proper control of the observations are provided.

   (*a*) Patients with early syphilis should not be subjected to an untried method of treatment.

   (*b*) The toxicity of the drug for man should be determined by giving, at the outset, one twentieth of the theoretical dose determined by animal experiment to patients with late syphilis, preferably those who have had previous treatment, and only when the patient consents to the trial of a new drug. If no reactions occur, the dose may be increased.

   (*c*) The effect on the serologic titer and on mensurable lesions of late syphilis should be observed. If these are favorable, trial on patients with early syphilis is justified.

6. In treating patients with early syphilis with a drug under trial:

   (*a*) The rapidity of disappearance of S. pallida from lesions should be observed.

   (*b*) The rapidity of healing should be noted and compared with that in patients under established systems of treatment.

   (*c*) The serologic titer should be followed and similarly compared.

   (*d*) Patients treated with a new drug should have a particularly careful, long follow-up with regard to clinical or serologic relapse.

Mercury.—Dissatisfied with the evidence on which bismuth has been adjudged more potent than mercury in the treatment of syphilis, Cannon and Robertson [34] sought to reexamine the subject. Unfortunately, their series was small, their controls were inadequate and they chose for comparison preparations of heavy metals which are not generally conceded

34. Cannon, A. B., and Robertson, J.: The Choice of Bismuth or Mercury with Arsphenamine in the Treatment of Early Syphilis, J. A. M. A. **106**:2133 (June 20) 1936.

to be the most effective (an oil suspension of sodium potassium bismuth tartrate and an oil suspension of mercuric salicylate). They state their conclusions as follows:

1. The salts of both metals have an important place in the antisyphilitic armamentarium. The various preparations selected—both of bismuth and of mercury—appear to have justified themselves in all cases examined in which the treatment was regular and the dosage adequate; but neither metal can compensate for the disadvantage of using an inferior arsphenamine preparation.

2. Mercury gives more brilliant but less uniform results than bismuth, so that in robust patients with a healthy excretory mechanism the body's natural defenses are perhaps more effectively stimulated by the mercurials. For patients less vigorous and for those who do not respond well to mercury preparations, bismuth offers a valuable substitute.

3. Arsphenamine can be counted on to deliver the strongest initial attack against Spirochaeta pallida and acts to best advantage when reinforced by one of the heavy metals; but if for any reason an arsphenamine is contraindicated, bismuth will probably give the better performance alone.

4. For those who would minimize the chances of ill effects and for those who hold that the parasite may become drug fast, alternating the two metals offers an obvious advantage.

Bismuth.—As was forecast,[1] a bismuth preparation intended for oral administration has been introduced under the name bismutrat and unfortunately has been exploited in a way which leaves much to be desired. Careful studies of its applicability in rabbit syphilis have been made, however, by Rein and Sulzberger [35] and by Kemp and Rosahn.[36] Rein and Sulzberger observed only a small group of animals and themselves recognize that their conclusions are therefore subject to some question, but they were sufficiently impressed with the action of bismutrat in rabbit syphilis to consider further experimental work advisable. Kemp and Rosahn, however, found that twenty-four daily doses each of bismutrat containing 20 mg. per kilogram of metallic bismuth failed to alter materially the course of early syphilis in 5 of 6 animals treated, and similar administration of doses of 50 mg. per kilogram apparently suppressed the infection in 2 of 4 animals but cured none. Similar experiences were noted with the oral administration of bismuth sodium iron citrate and bismuth and potassium tartrate. Important as are these observations, the greatest contribution made by these authors was their

35. Rein, C. R., and Sulzberger, M. B.: Bismuth by Mouth in the Treatment of Syphilis: A Preliminary Experimental Study with Bismuth Chloride (Bismutrate) in Rabbit Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **20**:125 (March) 1936.

36. Kemp, J. E., and Rosahn, P. D.: The Oral Administration of Bismuth in the Treatment of Experimental Rabbit Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **20**:131 (March) 1936.

emphatic restatement of the fact that by virtue of the entirely different chemical conditions existing in the gastro-intestinal tracts of the rabbit and man, the rabbit is entirely unsuited for the evaluation of preparations intended for oral administration in the treatment of syphilis in man. Finally, they conclude: "Until there is available a more adequate method of determining the value of this form of treatment, it is unwise to suggest the oral use of bismuth salts in the treatment of late syphilis, and reprehensible to suggest their use in the treatment of early syphilis."

Kolmer [37] investigated the possibility of administering bismuth by inunction by rubbing daily 50 mg. per kilogram of bismuth and potassium tartrate into the backs of normal and syphilitic rabbits. No toxic symptoms developed after six weeks of this treatment in the former group, and no influence on the course of events was noted after four weeks of treatment in the rabbits with syphilis.

Thio-Arsene.—Utilizing the patented method of Kharasch for the production of thioarsenites from the combination of an arsenoxide with a thio acid, Eckler and Shonle,[38] in an investigation of twenty compounds, found one, disodium bis (parasulfophenyl) (acetamidophenyl)-dithio-arsenite, which for the sake of brevity they called thio-arsene, which from preliminary study seemed worth investigating further. The present paper details and satisfactorily reports the chemical and basic pharmacologic investigations necessary before considering a new arsenical in the treatment of syphilis in man. Clinical investigation of the drug was undertaken by three groups. Becker and Obermayer [39] substituted thio-arsene for arsphenamine in a conventional arsphenamine-bismuth system of treatment, and on the basis of 4,000 injections given to 291 patients with various forms of syphilis they conclude: "The advantage of low arsenical content, along with good trypanocidal efficiency and low toxicity, coupled with the fact that the drug is available in solution in ampules, entitles thio-arsene to serious consideration in syphilotherapy in combination with bismuth." They observed gastro-intestinal reactions in from 20 to 30 per cent of their patients but state that the incidence of such reactions was reduced more than 50 per cent by slowing the rate of injection. Jaundice was observed in 8 patients; no other reactions occurred.

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37. Kolmer, J. A.: Inunctions of Bismuth in the Treatment of Experimental Syphilis of Rabbits, J. Chemotherapy **12**:278 (Oct.) 1935.

38. Eckler, C. R., and Shonle, H. A.: A Preliminary Study of Thio-Arsene, Disodium Bis (P-Sulfophenyl) (Acetamidophenyl)-Dithio-Arsenite, Am. J. Syph. & Neurol. **19**:495 (Oct.) 1935.

39. Becker, S. W., and Obermayer, M. E.: Clinical Observations on the Treatment of Syphilis by a Combination of Bismuth Salicylate and a New Arsenical Synthetic: A Preliminary Report, Am. J. Syph. & Neurol. **19**:505 (Oct.) 1935.

Connor and his co-workers [40] employed the drug alone for the treatment of patients with various stages of syphilis and discovered that it was not well tolerated; less than half of 206 patients studied for tolerance were able to stand doses of 5 cc. or more. No serious reactions, however, were encountered. The clinical results were unsatisfactory in 12 (24 per cent) of 49 patients with early syphilis, and in 10 of 27 patients S. pallida was found in the lesions by dark field examination on the third day after treatment was begun. They conclude:

> Thio-arsene does not possess a high degree of therapeutic efficiency even when administered biweekly in the highest tolerated doses.
>
> It is probably not a suitable drug for the treatment of syphilis, especially since more efficient and better tolerated drugs are at hand.
>
> In drawing the above conclusions as regards the therapeutic efficiency of thio-arsene, it is to be emphasized that they are data based on the use of thio-arsene alone and not on data of thio-arsene combined with other forms of therapy.

Robinson and Moore [41] report an even less happy experience, which is summarized as follows:

> In the form in which thio-arsene was supplied to us, its use was followed by such a high incidence of severe gastro-intestinal reactions as to necessitate marked reduction of the advised dose; and even with this reduction in dosage, severe though not serious gastro-intestinal reactions occurred in such a large proportion of cases as to render patients unwilling to continue treatment with the drug. Thio-arsene is not utilizable in patients who have previously been sensitized to the arsphenamines. In our hands a fresh dermatitis was provoked by thio-arsene in seven of eleven such patients. As to therapeutic efficacy, thio-arsene compares unfavorably with any of the arsphenamines or with bismuth as to its effect on the disappearance of surface organisms, on the healing of lesions, and on the blood Wassermann reaction.
>
> It is, we believe, unwise to draw conclusions as to the efficacy of any anti-syphilitic drug when used in combination with any other. In order to prove the efficacy of thio-arsene used in combination with bismuth, the procedure followed by Becker and Obermayer, it would be necessary to study the results of treatment in a similar and parallel series of patients treated with bismuth alone. This has not been done. In our opinion, the favorable results secured with the thio-arsene-bismuth combination employed by Becker and Obermayer are probably largely attributable to bismuth rather than to thio-arsene. Thio-arsene, in its present form, is not entitled to serious consideration in syphilotherapy.

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40. Connor, W. H.; Shaw, H. C.; Levin, E. A., and Palmer, R. B.: The Therapeutic Value of Thio-Arsene: A Clinical Study of the Therapeutic Efficiency and Toxicity of Disodium Bis (P-Sulphophenyl) (Acetamidophenyl)-Dithio-Arsenite, Based on 2,282 Injections Administered to 251 Patients with Syphilis, Am. J. Syph. & Neurol. **19**:514 (Oct.) 1935.

41. Robinson, H. M., and Moore, J. E.: The Treatment of Syphilis with a New Arsenical Drug (Thio-Arsene), Am. J. Syph. & Neurol. **19**:525 (Oct.) 1935.

Mapharsen.—The basic work of Tatum and Cooper [42] referred to in the previous review [1] has been followed by detailed pharmacologic study by two groups, Raiziss and Severac [43] and Gruhzit.[44] These investigators, working independently, arrived at essentially similar figures for the curative index of mapharsen in trypanosomiasis in rats (7.2 and 9, respectively); but whereas Gruhzit found a therapeutic index of 7 for mapharsen in rabbits with syphilis, Raiziss and Severac obtained the low figure of 0.92. The latter, therefore, concludes: ". . . the clinical use of this drug in adequate curative doses might be fraught with considerable danger."

Since Gruhzit's results indicated a superiority over the brand of neoarsphenamine with which it was contrasted (a curative index for syphilis in rabbits of 4 for mapharsen and 3.75 for neoarsphenamine in single dose, but 4.6 and 1.67 for the two drugs, respectively, in multiple doses) several groups of clinicians deemed it worthy of clinical trial; one report of these trials has appeared. Foerster and his associates [45] report eighteen months' experience with mapharsen, during which 4,666 intravenous injections of the drug were given to 233 persons with syphilis and 133 injections were given to 41 normal subjects or sufferers from other diseases. Studies on the excretion of arsenic revealed no undue retention, and dark field follow-up study of lesions in which S. pallida had been demonstrated revealed a disappearance of surface organisms usually in twenty-four hours. Healing of visible lesions was prompt, and the serologic response of patients with early syphilis was good. Clinical and serologic relapse were observed in general only after irregular or obviously inadequate therapy or in cases of involvement of the neuraxis. The drug was well tolerated; no nitritoid reactions were observed, and the only immediate reactions were mild gastrointestinal disturbances. Jaundice developed in 4 patients. These authors conclude, therefore, that mapharsen is a potent antisyphilitic agent and should be given an extensive, long time study.

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42. Tatum, A. L., and Cooper, G. A.: An Experimental Study of Mapharsen (Meta-Amino-Para-Hydroxy Phenyl Arsine Oxide) as an Antisyphilitic Agent, J. Pharmacol. & Exper. Therap. **50**:198, 1934.

43. Raiziss, G. W., and Severac, M.: Comparative Chemotherapeutic Studies of "Arsenoxide" (3-Amino-4-Hydroxy-Phenyl-Arsenoxide) and Neoarsphenamine, Am. J. Syph. & Neurol. **19**:473 (Oct.) 1935.

44. Gruhzit, O. M.: Mapharsen ("Arsenoxide") in the Therapy of Experimental Syphilis and Trypanosomiasis, Arch. Dermat. & Syph. **32**:848 (Dec.) 1935.

45. Foerster, O. H.; McIntosh, R. L.; Wieder, L. M.; Foerster, H. R., and Cooper, G. A.: Mapharsen in the Treatment of Syphilis, Arch. Dermat. & Syph. **32**:868 (Dec.) 1935.

UNTOWARD EFFECTS OF TREATMENT [46]

In a general article Rajam [47] reports his experience with reactions and complications in the course of the administration of 24,550 doses of neoarsphenamine to 7,160 East Indians with syphilis. His statement that this race does not tolerate neoarsphenamine well is borne out by his figures. Dermatitis was produced in 1 of each 126 patients treated, and the ratio of incidence was 1 to 147 for men and 1 to 83 for women. The individual dose of neoarsphenamine never exceeded 0.3 Gm.; yet there was 1 case of dermatitis for each 431 injections: 1 to 514 for the men and 1 to 264 for the women. There were 3 deaths. Jaundice, however, was less than half as common, but in this series hemorrhagic encephalitis developed in 6 cases.

After a somewhat similar study van Putte [48] reports that 10 per cent of his patients at the Batavia Hospital showed cutaneous reactions or allergic phenomena, usually after the third injection of neoarsphenamine.

Bismuthia.—Lueth and his co-workers [49] report a dramatic case of extensive pigmentation of the skin resembling argyria. The patient had for many years taken large quantities of bismuth salts by mouth for the treatment of gastro-intestinal disease. Bismuth was demonstrated by biopsy of the skin. Gougerot and Blum [50] report a similar case in a patient who had been receiving a bismuth compound intramuscularly for the treatment of syphilis over a period of five years.

Bismuth Erythroderma.—Nicolas, Rousset and Colas [51] review the meager literature on dermatitis following the intramuscular administration of a bismuth compound and add a report of a man of 39 who had severe erythroderma after the eighth dose of bismuth.

Bismuth Arthralgia.—Genner [52] noted the frequency of complaints of pains in the joints, usually multiple, in patients under antisyphilitic

46. A large number of individual cases of well recognized complications of treatment have been reported which are not included here.

47. Rajam, R. V.: Some of the Major Complications in Treatment of Syphilis, Indian M. Gaz. **70**:661 (Dec.) 1935.

48. van Putte, P. J.: Sensibilisatiestoornissen door neosalvarsaan tijdens de antisyphilitische Kuur, Nederl. tijdschr. v. geneesk. **80**:2133 (May 16) 1936.

49. Lueth, H. C.; Sutton, D. C.; McMullen, C. J., and Muehlberger, C. W.: Generalized Discoloration of Skin Resembling Argyria Following Prolonged Oral Use of Bismuth, Arch. Int. Med. **57**:1115 (June) 1936.

50. Gougerot, H., and Blum, P.: Imprégnation bismuthique cutanée générale: Pseudoargyrie cutanée provoquée par le bismuth, Bull. Soc. franç. de dermat. et syph. **42**:276 (Feb.) 1935.

51. Nicolas, J.; Rousset, J., and Colas, J.: Bismuth erythrodermia, Bull. Soc. franç. de dermat. et syph. **43**:9 (Jan.) 1936.

52. Genner, V.: Arthralgic Symptoms in the Course of Therapy of Syphilis with Arsphenamine and Bismuth, Nord. med. tidskr. **10**:1753 (Nov. 2) 1935.

treatment, and by a combination of clinical observation and statistical research he concludes that this must be regarded as a complication of bismuth therapy.

Arsphenamine Jaundice.—Sager [53] reports 99 cases of postarsphenamine jaundice, and in a long discussion of the various hypotheses as to etiology which have been advanced, he concludes that the jaundice is related to arsphenamine therapy. If syphilis plays any rôle, it must do so rarely, in his opinion; and while he believes that catarrhal jaundice and postarsphenamine jaundice are not etiologically related, he is willing to concede that there may be summation of the two conditions.

Hepatic Complications.—Using the rose bengal method, Kellogg, Epstein and Kerr [54] studied the hepatic function of 90 patients with syphilis before and during antisyphilitic therapy. Thirty-eight patients had early syphilis, 35 had latent syphilis and 17 suffered from various forms of late syphilis. In 20 of the 90 the result of the rose bengal test was abnormal before treatment was begun, but there was no correlation between this finding and the type of syphilis involved. In 17 of the 20 there were no other signs of hepatic dysfunction, and the results of the rose bengal test were more nearly normal after antisyphilitic therapy in 10 but remained abnormal in 7. The one patient with clinically recognizable cirrhosis of the liver who received arsenical therapy tolerated it poorly. Routine antisyphilitic therapy occasioned a decrease in the excretion of rose bengal in 5 of 29 normal patients who were followed through treatment and accentuated a preexisting hepatic dysfunction in 4 of 18 patients.

Fat Embolism Following Treatment with Bismarsen.—Swartz, Tolman and Levine [55] report the instance of a patient who, immediately after the third dose of bismarsen became weak, pale and nauseated and a few minutes later had a chill, complained of backache and went into shock. Deep jaundice developed in a few hours, and there were purpuric manifestations and a high grade of nitrogen retention. The patient died twenty hours after the injection. At autopsy little was to be seen grossly, but microscopic study revealed the typical picture of fat embolism.

Intravenous Testing for Arsphenamine Sensitivity.—Dissatisfied with the unreliability of the patch test (especially when negative results

53. Sager, R. V.: Factors Responsible for Jaundice in Syphilis, with Special Reference to the Rôle of the Arsphenamines, Arch. Int. Med. **57**:666 (April) 1936.

54. Kellogg, F.; Epstein, N. N., and Kerr, W. J.: Hepatic Complications in the Treatment of Syphilis: II. Incidence of Hepatic Disease in Patients with Untreated Syphilis and During Their Subsequent Treatment, Ann. Int. Med. **9**:1561 (May) 1936.

55. Swartz, J. H.; Tolman, M. M., and Levine, H.: Fatality Following Bismarsen Therapy, Arch. Dermat. & Syph. **33**:874 (May) 1936.

are obtained) in determining the question of the advisability of further arsenical therapy for patients with a history of postarsphenamine dermatitis, Robinson [56] examined the feasibility of intravenous testing on 110 such patients. At least three months after the dermatitis had subsided each patient was given intravenously 0.025 Gm. or less of a different member of the arsphenamine group than the one which was given preceding the reaction and was carefully observed. If the drug was well tolerated, a week later the dose was doubled, and so on until a therapeutic dose was reached. At any stage subjective or objective cutaneous reactions constitute a positive reaction and preclude proceeding further. The most strongly positive reactions were sufficiently mild to occasion the patient no harm and little discomfort.

Forty-four of the patients tested had also had patch tests made; the comparative results are presented for 41. Seven of the 8 who showed a positive result of the patch test and also 21 of the 33 who showed a negative result of the patch test gave a positive reaction to intravenous testing. There were 66 patients tested intravenously who had not had patch tests. Of these, 34 gave negative reactions, and arsphenamine therapy was resumed without event; 21 gave strongly positive reactions, and a group of 11 patients, who at first gave mildly positive reactions, on repetition of the test failed to react.

From this experience the author concludes that a strongly positive reaction to a patch test precludes the further administration of any of the arsphenamines, but that a weakly positive or negative result of a patch test demands that intravenous testing be carried out before a final decision is made regarding the advisability of further arsphenamine therapy.

Intracranial Hemorrhage After Cisternal Puncture.—Weissenbach and his collaborators [57] report the instance of a patient on whom, a first attempt at cisternal puncture having been unsuccessful, a successful puncture a few minutes later revealed bloody fluid. A severe meningeal reaction developed, but recovery ensued. This occasioned a review of the literature, from which the investigators concluded that there are about 2 serious or fatal complications for every 1,000 cisternal punctures performed, an incidence too high to justify utilization of the method as a routine procedure.

Dandy [58] reports the operative treatment in a similar situation. Technically perfect cisternal puncture revealed a freshly bloody fluid;

56. Robinson, H. M.: Intravenous Testing in Postarsphenamine Dermatitis, South. M. J. **29**:411 (April) 1936.

57. Weissenbach, R. J.; Bocage, A., and Block-Michel, H.: Hémorragie méningée au cours d'une ponction sous-occipitale, Bull. Soc. franç. de dermat. et syph. **42**:785 (May) 1935.

58. Dandy, W. E.: The Treatment of Intracranial Hemorrhage Resulting from Cisternal Puncture, Bull. Johns Hopkins Hosp. **56**:294 (May) 1935.

within half an hour the patient complained of headache and drowsiness and shortly thereafter lapsed into coma. Two and a half hours after the puncture he was desperately ill; four hours later craniotomy was performed, and the bleeding point was cauterized, with eventual recovery. At operation it was discovered that the cerebellar tonsils lay much farther down than usual and so had practically obliterated the cisterna. This resulted in placing a posterior inferior cerebellar artery directly in the normal course of the needle. Anatomic study revealed that this is not an unusual anomaly, so Dandy concludes that cisternal puncture carries with it an unavoidable risk.

THE PROPHYLAXIS OF SYPHILIS

Bismuth Prophylaxis.—Inspired by empirical reasoning and encouraged by the experimental work of Levaditi and his collaborators, previously mentioned,[1] Sonnenberg [59] has for nine years been practicing the bismuth prophylaxis of syphilis among prostitutes. His method comprises the weekly injection of 1 cc. or more usually, the biweekly injection of 2.5 cc. of a 10 per cent suspension of bismuth subnitrate in oil. Twenty-seven of the 327 prostitutes so treated and observed for more than five years have acquired syphilis, in every instance before the fourteenth week of biweekly treatment. Since syphilis is practically universal among the prostitutes of his district, Sonnenberg feels that his experience is absolutely proof of the efficacy of bismuth prophylaxis, and since all the cases of infection occurred before the fourteenth week (the seventh treatment) he concludes that approximately 7 injections of the magnitude he employed are necessary to insure that the tissue bismuth is at a prophylactic level.

Lépinay [60] reports a similar experience on a smaller scale; 38 of 40 persons were protected for periods up to twenty-seven months of regular treatment. He shows, however, that, irrespective of the amount of previous treatment, prophylactic efficiency lasts for only about twenty days after the last injection. Levaditi and his group of workers [61] have continued the experimental work previously commented on [1] but have added nothing new. Levaditi [62] has been urging further clinical trial of the method.

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59. Sonnenberg, E.: Neuf ans de traitement préventif bismuthique de la syphilis, Bull. Acad. de méd., Paris **114**:374, 1935.

60. Lépinay: Essais de préservation de la syphilis par bismutho-prevention chez les prostituées d'un "quartier réservé," Prophylax. antivén. **8**:230 (April) 1936.

61. Levaditi, C.; Manin, Y.; Seveaux, A., and Vaisman, A.: Recherches sur la metalloprévention de la syphilis l'arsénic, Bull. Soc. franç. de dermat. et syph. **42**:1624 (Nov.) 1935.

62. Levaditi, C.: La metalloprévention de la syphilis, Prophylax. antivén. **8**: 195 and 235 (April) 1936.

Mercury Prophylaxis.—Schereschewsky [63] advances the opinion that mercury is valueless for the prophylaxis of syphilis but states that he has found a 40 per cent ointment of quinine hydrochloride to be unfailing. Millspaugh,[64] however, in a better documented communication reemphasizes the time factor in the prophylaxis of syphilis and corroborates the experiences during the World War that apparent failures of prophylaxis with mercury are traceable to too long an interval between the first exposure and the prophylaxis. Mahoney,[65] in an important paper which is too long to review here in detail, subjected the matter of prophylaxis to experimental resurvey. By three methods of investigation he demonstrated that actual invasion of the mucosa of the penis of the rabbit by the organism after exposure to the virulent emulsion of S. pallida took place between the second and the third hour after exposure began; prior to that the organism lay on the surface and could easily be destroyed by antiseptics, and almost as readily by soap and water. Ointment of mild mercurous chloride (in large amounts) served to protect animals from infection if applied before or immediately after exposure and was almost as effective when rubbed into the back as when applied to the area which had been exposed to infection.

THE TREATMENT OF EARLY SYPHILIS

In 1928 the Health Organization of the League of Nations sponsored a statistical investigation of the results of the treatment of syphilis in clinics of five countries—France, Germany, Denmark, Great Britain and the United States. The method of gathering material and the plan of study were identical with those of the Cooperative Clinical Group.[1] Ninety-four clinics in these five countries contributed 25,623 case records for analysis. This material was reviewed under Martenstein's [66] able direction, and a report is submitted, based primarily on the results of treatment of 13,198 patients with early syphilis for whom complete information was furnished. In summarizing the experience Martenstein says:

> I would therefore repeat once more the unexpectedly clear result that has emerged from this statistical compilation.
>
> The methods of treating primary, and early and late secondary syphilis to be recommended as the most successful at the present day are:
>
> 1. The continuous method of treatment as such;
> 2. The intermittent method of treatment, as carried out in Denmark or Great Britain.

63. Schereschewsky, J.: Prophylax. antivén. **8**:220 (April) 1936.

64. Millspaugh, J. A.: Prophylaxis of Venereal Disease, U. S. Nav. M. Bull. **34**:32 (Jan.) 1936.

65. Mahoney, J. F.: An Experimental Resurvey of the Basic Factors Concerned in Prophylaxis in Syphilis, Mil. Surgeon **78**:351 (May) 1936.

66. Martenstein, H.: Syphilis Treatment: I. Enquiry in Five Countries, Quart. Bull. Health Organ, League of Nations **4**:129 (March) 1935.

It should be specially emphasized that particularly satisfactory treatment results were also obtained in a number of clinics in the other countries, and when the methods which they use are compared, they are found to agree in striking fashion with those applied in Denmark and the United Kingdom.

In making up their final recommendations the committee, composed of Jadassohn, Madsen, Harrison, Gougerot, Lomholt and Stokes, took into consideration the fact that in the systems of intermittent treatment used in Denmark and Great Britain an arsphenamine and a heavy metal are given in concurrent courses, separated by only short rest periods, so that, *in effect, the patient is receiving essentially continuous treatment by absorbing heavy metal from his intramuscular stores during the brief rest periods.* Their final conclusions follow:

1. Treatment should be recommended as early as possible in the sero-negative primary stage. In this connection, the fullest possible use should be made, for purposes of diagnosis, of the microscopical examination of secretions from primary lesions or from lymph glands.

2. It should be emphasized that, prior to the institution of either of the systems of treatment outlined below, there should be an adequate physical examination to determine the absence or otherwise of any indication for caution in respect of the dosage.

3. It is essential that, in carrying out the treatment, a strict supervision of the patient be exercised, especially in respect of mucous membranes, skin, kidneys and liver.

4. Observation, clinical and serological, after completion of treatment should be adequate and in any case for not less than three years.

5. Adequate examination of the spinal fluid, at least before dismissal from observation, is essential.

6. The principles to be followed in carrying out the actual treatment should be as follows:

(*a*) To employ a comparatively heavy individual dosage of the arsenobenzene and of the bismuth or mercurial compounds, the doses being administered in comparatively rapid succession, especially at the commencement;

(*b*) To maintain a persistent attack on the disease, avoiding intervals of such length as to afford the parasite an opportunity of recovering;

(*c*) To administer approximately as much treatment to primary as to secondary cases.

7. The material studied does not enable a clear decision to be made as to the relative merits of intermittent treatment with courses of injections in rapid succession separated by rest intervals of some weeks and continuous treatment . . . or between the simultaneous employment of both arsenical and bismuth or mercury, and the system in which bismuth and mercury are withheld until a number of arsenical injections have been administered.

Nevertheless, it seems practicable, from the results of the analysis and from the personal experience of the Experts, to formulate a system of intermittent treatment and one of continuous treatment, either of which can be expected to yield satisfactory results in ordinary cases of early syphilis.

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67. Footnote deleted by the author.

It seems possible that the intermittent treatment which is suggested below may in effect be continuous, or practically continuous, treatment, owing to the continued absorption of bismuth from the sites of the injection for some weeks after any temporary suspension of the treatment.[68]

The Fever Therapy of Early Syphilis.—Neymann, Lawless and Osborne[69] provide the latest report on the fever treatment of early syphilis. These authors treated 14 patients with early syphilis by means of from 3 to 8 bouts of fever; 7 of them also received either concurrently or immediately afterward, a short course of an arsphenamine and bismuth. All the patients who did not receive supplementary chemotherapy had a relapse; those who had this totally inadequate treatment with neoarsphenamine and bismuth have been well for periods varying from five to eighteen months.

The remainder of the recent literature on this subject has been the subject of editorial comment.[70]

In the *Journal of the American Medical Association* issue of Dec. 28, 1935, Simpson[71] reports the results of the treatment of early syphilis, latent Wassermann-fast syphilis, and neurosyphilis with artificial fever in combination with chemotherapeutic agents. Since the value of fever in the treatment of neurosyphilis is fully established and since the studies of the Cooperative Clinical Group have shown that the results of chemotherapeutic treatment of latent Wassermann-fast syphilis are satisfactory without fever therapy, his report is of interest mainly because of his use of fever in the treatment of twenty-six patients with early syphilis.

These twenty-six patients were treated with a total of 9 Gm. of neoarsphenamine and 6 Gm. of bismuth during a period of thirty weeks, supplemented by fever maintained above 105 F. for thirty hours. They were followed for six to thirty months after treatment ended, and within this period of time the outcome was judged to be more satisfactory than in two control groups: one of six patients treated with fever only and the other of fourteen patients treated with thirty weeks of chemotherapy only. Simpson thought these results "to provide evidence that fever therapy may be of great value in early syphilis, particularly when chemotherapy alone appears inadequate."

In his discussion of Simpson's paper, Stokes points out that as a result of the Cooperative Clinical Group's studies we now have a highly satisfactory plan of treatment for early syphilis, which has been evaluated by the study of an unusually large group of patients. He urged that the position of this treatment plan be not jeopardized by attempts to apply a new and untried method which demands a high degree of specialization. Stokes's remarks are of sufficient importance to warrant further emphasis.

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68. The italics have been supplied by us.

69. Neymann, C. A.; Lawless, T. K., and Osborne, S. L.: The Treatment of Early Syphilis with Electropyrexia, J. A. M. A. **107**:194 (July 18) 1936.

70. The Fever Treatment of Early Syphilis, editorial, Am. J. Syph., Gonor. & Ven. Dis. **20**:445 (July) 1936.

71. Simpson, W. M.: Artificial Fever Therapy of Syphilis, J. A. M. A. **105**: 2132 (Dec. 28) 1935.

The plan of treatment for early syphilis recommended by the Cooperative Clinical Group was not evolved suddenly from their preconceived ideas of how early syphilis should be treated but was arrived at from an extensive study and comparison of the various treatment schemes which have been proposed since the discovery of arsphenamine. The history of the development of the scheme is of interest in emphasizing this point. In 1916, seven years after the introduction of arsphenamine in the treatment of syphilis, it occurred independently to Keidel [72] in this country and to Almkvist [73] in Europe that the unsatisfactory results of the treatment of early syphilis with the arsphenamines were due to the physician's lack of a clear understanding of what he was attempting to accomplish. They felt that patients with early syphilis might be biologically "cured" if treatment was continued *without interruption* for a sufficient length of time and if, in order to avoid drug resistance, mercury was used in alternation with the arsphenamines. Almkvist decided that a year of continuous treatment was necessary, and Keidel decided upon a year of treatment after the permanent reversal of the blood Wassermann. In 1932 the Cooperative Clinical Group,[74] evaluating a great variety of treatment schemes for early syphilis, found that the majority of patients with early syphilis were clinically and serologically "cured" if they were given a minimum of twenty injections each of one of the arsphenamines and a heavy metal without interruption for a year during the first two years of the infection. They, therefore, accepted as satisfactory essentially the same plan proposed by Almkvist and Keidel fifteen years before.

The authority of this great amount of material followed for so long a time precludes the adoption of other treatment schemes which have a less substantial background. This is particularly true of fever therapy for two reasons:

In the first place, fever and chemotherapy in the treatment of early syphilis has been tried and found less satisfactory than other treatment plans. Malaria combined with courses of neoarsphenamine was treated about fifteen years ago and was abandoned because the immediate satisfactory results (Kyrle [75]) were not confirmed by subsequent developments (Kerl [76]). There is at present such insufficient evidence that mechanical methods for producing fever have any advantage over the older method of malaria therapy that a reopening of the question seems inadvisable.

In the second place, the proposal to use hyperpyrexia jeopardizes the advances that have already been made in the treatment of early syphilis. The knowledge

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72. Moore, J. E., and Keidel, A.: The Treatment of Early Syphilis: I. A Plan of Treatment for Routine Use, Bull. Johns Hopkins Hosp. **39**:1, 1926. Moore, J. E., and Kemp, J. E.: The Treatment of Early Syphilis: II. Clinical Results in Four Hundred and Two Patients, ibid. **39**:16, 1926; III. The Wassermann Reaction in Treated Early Syphilis, ibid. **39**:36, 1926.

73. Almkvist, J.: Re Continuous Treatment of Syphilis Instead of Chronic Intermittent Treatment, Acta dermat.-venereol. **1**:97, 1920.

74. Stokes, J. H.; Usilton, L. J.; Cole, H. N.; Moore, J. E.; O'Leary, P. A.; Wile, U. J.; Parran, T., Jr., and McMullen, J.: Standard Treatment Procedure in Early Syphilis: A Résumé of Modern Principles, Ven. Dis. Inform. **15**:149, 1934; What Treatment in Early Syphilis Accomplishes, ibid. **15**:341, 1934.

75. Kyrle, J.: Die Malariabehandlung der Syphilis, Wien. klin. Wchnschr. **37**:1105, 1927.

76. Kerl, W.: Malariabehandlung der Frühlues, Arch. f. Dermat. u. Syph. **157**: 294, 1929.

that the treatment of syphilis requires at least a year has gradually been accepted by a small but appreciable part of the lay population. This knowledge has been gained very gradually during the past ten years from various sources, the most important of which have been the larger syphilis clinics. It has been disseminated for the most part by patients under treatment or observation for syphilis in these clinics. However, during the last four or five years, numerous articles concerning fever therapy have appeared in the lay press. They have varied from sane accounts of the use of fever in the treatment of disease [77] to stories of physicians using fever to produce a sturdier crop of corn.[78] The layman is unable to judge the value of these articles, and, as a result, the patient with early syphilis may become the victim of the less capable or the dishonest physician. If this happens, it will not be long before both patient and physician are as confused as they were in the years immediately following the advent of the arsphenamines. The long process of reevaluation of treatment schemes and reeducation of the patient will have to be begun afresh, and in the meantime it is to be feared that the incidence of early syphilis will continue to increase.

There are many who feel that the recent recognition of syphilis as one of our major public health problems will awaken the interest of the local health officer sufficiently to secure his aid in dealing with some of the problems which have so far prevented progress in the control of the disease. This cooperation will be of value chiefly in bringing patients with early syphilis under treatment. If this can be accomplished, there is at hand a plan of treatment which, if properly executed, will give extremely satisfactory results. It is hoped that these results will not be jeopardized by any treatment schemes which, whatever their potentialities, are at the present time unproved.[78a]

The Curability of Syphilis.—In regard to the attitude to be taken concerning the end-results to be achieved by modern methods of treatment, Klein [79] reemphasizes the caution necessary when an individual and not a group is under consideration, with particular reference to the suitability of a person with syphilis as a prospective marital partner and parent. Klein emphasizes, not too strongly, the necessity for any person with syphilis to submit to a lifetime of observation, but, in our opinion, he paints too gloomy a prospect of the eventual outcome for the marital partner and the children provided the proper follow-up regimen is observed.

TREATMENT-RESISTANT SYPHILIS

In a detailed review of the literature, which does not lend itself well for summary here, Beerman [80] points out that treatment-resistant syphilis

77. Fever as a Friend, Scient. Am. **153**:40, 1935.

78. Chicago Daily News, Feb. 19, 1936, p. 11.

78a. In addition to the articles cited are numerous general discussions of the treatment of early syphilis which contain nothing new and so are not proper material for review here but which by their wide distribution in general journals have served the useful purpose of widely publicizing modern methods of treatment.

79. Klein, J. E.: The Curability of Syphilis, Arch. Dermat. & Syph. **33**: 1055 (June) 1936.

80. Beerman, H.: The Problem of Treatment-Resistant Syphilis, with Special Reference to Arsphenamine-Resistant Syphilis: Review of the Literature and Experimental Study, Am. J. Syph., Gonor. & Ven. Dis. **20**:165 (March); 296 (May) 1936.

has been variously defined but that no single definition is entirely satisfactory. He says:

> The essential criteria of treatment-resistant syphilis are: (*a*) persistence of lesions, (*b*) persistently positive blood serologic tests and (*c*) persistence of spirochetes in spite of usually adequate treatment. Of these three the persistence of Spirochaeta pallida in the lesions is the most reliable criterion of treatment-resistance in human syphilis.

It is emphasized that resistance to treatment is a phenomenon of any stage of syphilis, but since the most characteristic lesions are cutaneous and occur in early syphilis, these have been most spoken of, and less attention has been paid to the more fundamentally important questions of visceral lesions Beerman thinks that the classifications of resistance to treatment which previously have been suggested are meaningless.

The observations that the serologic reaction for syphilis in patients with treatment-resistant early syphilis tends to be negative or prematurely to revert to negative and that many of these patients react badly to the arsphenamines are carefully restated. In a detailed discussion of the evidence, this author concludes further that:

> The consensus at present seems to regard the host as the factor most responsible for treatment-resistant syphilis. While a number of studies have indicated that under certain conditions Spirochaeta pallida may be made to develop a certain degree of resistance to antisyphilitic drugs, no one up to the present has reported the transfer of Spirochaeta pallida from a treatment-resistant syphilis in man to rabbits with preservation or demonstration of treatment resistant characteristics in the rabbits.

A case of treatment-resistant syphilis is reported, and the methods of therapy to be employed in such cases are discussed in detail. Finally, spirochetes from the patient were transferred to rabbits, and the disease produced was compared with that produced by the Nichols strain. In general the lesions produced by the fresh strain were less conspicuous, and larger doses of arsphenamine were required to effect a cure in rabbits than was usual with the Nichols strain.

Greenbaum and Rule [81] reach essentially the same conclusions from a review of the literature and report efforts to produce drug resistance in the Nichols strain of S. pallida. Through nine passages animals that had been given injections of the strain were treated with subcurative doses of neoarsphenamine before transfer. The animals which were infected by injection at the ninth passage were cured as readily as controls.

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81. Greenbaum, S. S., and Rule, A. M.: Resistant Syphilis, with Especial Reference to an Attempt to Produce Experimentally an Arsenic-Resistant (Neoarsphenamine-Resistant) Strain of Spirochaeta Pallida, Pennsylvania M. J. **39**: 339 (Feb.) 1936.

In regard to the part played by the host and the organism in the development of resistance to treatment, MacCormac [82] reports an instance in which both a woman and the man by whom she had been infected had treatment-resistant syphilis. This, naturally, is adduced by the author as proof that the organism is the origin of resistance to treatment.

Serologic Resistance.—Morgan [83] reviews the subject of serologic resistance (so-called Wassermann fastness) and concludes that while the persistence of positive serologic reactions after treatment necessitates the making of further investigations, "in late latent syphilis treatment need not be continued on account of positive serologic reactions alone."

CLINICAL PHENOMENA IN EARLY SYPHILIS

Association with Gonorrhea.— The common experience of discovering a positive reaction to the serologic test for syphilis or late lesions of the disease in a patient who can give no history of early syphilis but who has had gonorrhea has led many to assume that coexisting gonorrhea can mask the lesions of early syphilis. In this regard the report of Kemp and Shaw [84] is of great interest. These authors carefully examined and made follow-up serologic tests on 500 men and 500 women with acute gonorrheal urethritis. Seven men and 15 women were discovered to have primary syphilis; 6 men had noted the lesion before its discovery by the physician, and in all the patients of both sexes the nature of the lesion was clinically provable. Similarly, only 3 of 19 patients with secondary syphilis were unaware of the eruption. There were 114 other patients with latent or late syphilis at the time of admission, but follow-up serologic tests did not reveal any symptomless infection among the patients without lesions and with a negative reaction to serologic tests for syphilis when they were first seen.

Extragenital Primary Syphilis.—In a review of the literature Wagener [85] discovered 7 reports of large series of patients with primary syphilis; in these the incidence of extragenital infection varied from 2.5 to 15.6 per cent. The average for the entire group was over 8 per cent. In his material 32 (11.5 per cent) chancres were extragenital,

82. MacCormac, H.: Arsenic Resistant Syphilis, Proc. Roy. Soc. Med. **28**: 1527 (Sept.) 1935.

83. Morgan, A. G.: The Significance of Resistant Serologic Reactions, Ven. Dis. Inform. **16**:379 (Nov.) 1935.

84. Kemp, J. E., and Shaw, C.: The Rôle of Acute Gonorrheal Urethritis in Masking the Lesions of Early Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **20**: 56 (Jan.) 1936.

85. Wagener, F.: Extragenitale syphilitische Primäraffekts an der Bonner Hautklinik seit 1924, Inaug. Dissert., Bonn, 1935.

being located as follows: on the right tonsil, the upper lip and the lower lip, each in 7 instances; on the left tonsil in 4 and on the nose in 2. There was 1 instance each of primary syphilis at the corner of the mouth, on the tongue, on the eyelid, on the ring finger and about the anus. From follow-up studies the author concludes that, aside from the site of infection, no phenomena differentiated this group from other patients with early syphilis.

Tobias [86] provides a similar report of 65 patients with extragenital chancres and discusses at length the source of infection and the means of transmission, with the public health problems involved. The location of the lesion in this group was as follows: upper lip, 20; lower lip, 16; tonsil, 1; tongue, 6; cheek, 3; nose, 2; right index finger, 7; right middle finger, 2; breast (female), 3; breast (male), 1; scalp, 1, and chin, 3.

Reinfection.—Because of the close medical supervision of enlisted men in the navy, Millspaugh [87] has the opportunity to report 7 clearly proved cases of reinfection with syphilis. This he does primarily to show that these seamen had achieved a biologic cure of the first infection after antisyphilitic therapy, 1 with only 11 injections of neoarsphenamine and 16 of bismuth.

Transfusion Syphilis.—Mandelbaum and Saperstein [88] report the development of acute gummatous osteomyelitis as the first manifestation of transfusion syphilis, eight weeks after the transfusion. This, they point out, is unique, since in all other cases reported a generalized cutaneous eruption has developed within three and a half months after the offending transfusion.

LATE SYPHILIS

Treatment.—Greenbaum [89] reports his experience with acute late syphilis, which he defines as the eruptive stage of the second incubation period. When this stage of the disease has been reached, he believes that avoidance of therapeutic shock is sufficiently important to justify some prolongation of the patient's period of infectivity. Therefore, he advises and for several years has practiced the institution of therapy with bismuth.

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86. Tobias, N.: Extragenital Chancres: A Clinical Study, Am. J. Syph., Gonor. & Ven. Dis. **20**:266 (May) 1936.

87. Millspaugh, J. A.: Syphilitic Reinoculation, Mil. Surgeon **79**: 25 (July) 1936.

88. Mandelbaum, H., and Saperstein, A. N.: Transmission of Syphilis by Blood Transfusion: A Case of Acute Gummatous Osteomyelitis, J. A. M. A. **106**: 1051 (March 28) 1936.

89. Greenbaum, S. S.: The "Bismuth Approach" in the Treatment of Acute (Late) Syphilis, J. Chemotherapy **13**:5 (April) 1936.

Syphilis of the Bladder.—In a search of the literature since 1900 Finestone [90] discovered reports of 158 cases of syphilis of the bladder, which he analyzes in detail. He concludes:

There is marked laxity in the reporting of cases which are neither thoroughly studied nor followed and adequately controlled.

Only eight investigators have subjected the lesions to microscopic study. Only one shows typical histopathology. Two are claimed to have shown specific histopathology but are not reported in detail. The five others give descriptions of nonspecific inflammation.

Not one of the cases described measures up to the standard set by Young, who maintains that the spirochaeta must be demonstrated in the lesions.

To this he adds his own experience in 2 cases. One was typical of the group in which the diagnosis rests on the therapeutic test; the other apparently was typical of the same group, but later it was discovered that the patient had a tuberculous kidney, and the vesical lesion was thought to have been secondary to it.

In addition to the type of lesions with which Finestone was concerned, Kasztriner [91] reports on a series of patients with lesions of early syphilis who had symptoms of acute cystitis and in whom cystoscopic examination revealed erythematous syphilids, papules and ulcers. Because of the coexistence of cutaneous lesions and the prompt relief following treatment, this author believes the lesions represented early syphilis of the bladder, despite the fact that S. pallida could not be found. Kâmil [92] reports a similar case.

Syphilis of the Lung.—Takei [93] reports the case of a 48 year old Japanese laborer who was observed during an acute illness, which was characterized by pain in the right side of the chest, fever and productive cough. Because of the fact that he had syphilis and cutaneous gummas, that no tubercle or other bacilli or fungi could be found in the sputum and that antisyphilitic therapy was followed by critical defervescence, it was suggested that he had syphilis of the lung. Curious as to the validity of the diagnosis, the author collected reports of 95 cases from the literature in which the diagnosis of pulmonary syphilis had been based on the same criteria as his own and analyzed them for features in common. The ages of the patients varied widely, but most of them were in from the third to the sixth decade of life, and the average duration of syphilis had been eighteen years. There were two and three-tenths times as many men as women. In two thirds of the patients

90. Finestone, E. O.: Syphilis of the Bladder, Surg., Gynec. & Obst. **62**:93 (Jan.) 1936.

91. Kasztriner, I.: Syphilis of the Bladder, Ztschr. f. urol. Chir. **41**:477 (Feb. 12) 1936; abstr., Ven. Dis. Inform. **17**:217 (July) 1936.

92. Kâmil, F.: Blasenlues, Ztschr. f. Urol. **29**:163, 1935.

93. Takei, U.: Ueber Lungensyphilis, J. Orient. Med. **24**:10 (Jan.) 1936.

the lesion was in the right lung only; in a sixth each it was in the left lung or was bilateral. In only 3 per cent was the process at the apex of the lung. Complicating lesions of syphilis were present in the bones, heart, aorta, spleen and liver. The mortality rate was 34.7 per cent in the group of cases reported in the literature, but the author thinks that the prognosis is good if antisyphilitic therapy is given early.

Syphilis of the Stomach.—Pusch [94] studied 35 cases which had been reported in the literature as instances of syphilis of the stomach and discusses them in detail. Clinically, the differential diagnosis lay between syphilis of the stomach and cancer, and usually it had been impossible to reach a decision since the salient symptoms and findings are alike in the two conditions. It may be helpful, however, that syphilis of the stomach commonly occurs before the age of 40. This is not a dependable feature, however; and since neither serologic tests for syphilis nor an apparent response or lack of response to treatment should be relied on, operation should not be delayed for a therapeutic test, thereby running the risk of depriving a patient with an operable carcinoma of the benefits of surgical treatment. Even in syphilis of the stomach, operation is frequently necessary to relieve obstruction caused by scarring.

Williams [95] objects to the requirement that a lesion of the stomach may not be considered due to syphilis unless animal inoculation proves the presence of S. pallida. Such a requirement, he says, is not met in the diagnosis of other lesions of late syphilis. The diagnosis of gastrointestinal syphilis may be made, in his opinion, if the following criteria are fulfilled:

1. Roentgenologic evidence of smooth, tubelike gastric deformity.
2. Youth of the patient.
3. The presence of other evidences of syphilis.
4. Improvement under antisyphilitic treatment.
5. If an operation is performed, the discovery of an inflammatory mass.
6. The demonstration in excised tissue of lesions compatible with syphilitic inflammatory tissue.

CARDIOVASCULAR SYPHILIS

Unusual Findings.—Richter [96] reports the first recorded instance of the demonstration of S. pallida in an aortic cusp. The patient had also

94. Pusch, L. C.: Syphilis of the Stomach: A Review of Thirty-Five Selected Cases, Internat. Clin. **1**:56 (March) 1935.

95. Williams, C.: The Diagnosis of Syphilis of the Gastro-Intestinal Tract, Virginia M. Monthly **62**:322 (Sept.) 1935.

96. Richter, A. B.: Treponema Pallidum in Syphilitic Aortic Valvulitis of a Congenitally Bicuspid Valve with Subaortic Stenosis: Report of a Case, Am. J. Path. **12**:129 (Jan.) 1936.

congenital heart disease. Blackman [97] adds 2 cases to the solitary case previously reported of syphilis of the mitral valve and the membranous interventricular septum; both patients had syphilitic aortitis, with the typical anatomic picture of aortic insufficiency, and the process which involved the septum and the mitral valve was a direct continuation of the process in the root of the aorta, so it chiefly involved the anterior mitral segment. Sohval [98] describes 2 cases of gumma of the heart and reviews the 97 previously reported cases. The most frequent site for gumma of the heart is in the myocardium of the left ventricle, particularly at the base of the interventricular septum. In this location the process may interfere with the conduction system, and heart block may supervene. The diagnosis is seldom made clinically but should be suspected, according to Sohval, in the presence of "unusually situated, weird stenotic murmurs, unexplained roentgen shadows at the cardiac margins and heart block in a patient in whom syphilis is suspected . . ."

Syphilitic Aortitis in the Young.—In a review of the literature Norris [99] could find reports of only 12 cases of syphilitic aortitis in which the syphilitic infection could be either proved or reasonably assumed to be of congenital origin. To this experience he adds a report of 2 patients, a girl of 9 and a boy of 17, both of whom died suddenly and were found at autopsy to have typical syphilitic aortitis. Congenital syphilis was not proved in either instance, but in both it seemed most probable. In his discussion, Norris brings out that, since the precocious development of syphilitic aortitis only a few years after infection is acquired is well known, it cannot be said that such was not the case here, since congenital syphilis was not proved; but he is of the opinion that the assumption of the congenital nature of the infection is justified.

Syphilitic Myocarditis.—Magill [100] reports on a series of patients who presented a picture which he considers to be typical of syphilitic myocarditis. All were young (the oldest was 46), and all were suffering from moderate to severe degrees of cardiac decompensation unexplained by any of the usually accepted causes of cardiac disease. Aside from cardiac enlargement and the usual presence of a protodiastolic gallop rhythm, the examination of these patients revealed singularly little.

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97. Blackman, S. S., Jr.: Syphilis of the Mitral Valve and the Membranous Interventricular Septum of the Heart, Bull. Johns Hopkins Hosp. **57**:111 (Sept.) 1935.

98. Sohval, A. R.: Gumma of the Heart: Report of Two Cases, Arch Path. **20**:429 (Sept.) 1935.

99. Norris, R. F.: Syphilitic Aortitis in Childhood and Youth: Report of Two Cases with Sudden Death, Bull. Johns Hopkins Hosp. **57**:206 (Oct.) 1935.

100. Magill, T. P.: Syphilitic Myocarditis, Bull. Johns Hopkins Hosp. **57**:22 (July) 1935.

There was no arteriosclerosis, and the blood pressure was not elevated, but in most of them the pulse pressure was low; and there were no signs of organic valvular disease. All of these patients either showed a positive reaction to serologic tests for syphilis or gave a history of precedent antisyphilitic treatment.

Five came to autopsy; in none was there disease of the coronary arteries, but all manifested a uniform pathologic picture characterized microscopically by extensive scarring and round cell infiltration of the myocardium.

Abdominal Aneurysm.—Kampmeier [101] describes the clinical findings in 73 cases in which a diagnosis of abdominal aneurysm was made and the anatomic findings in the 38 that came to autopsy. Death was due to rupture of the aneurysm in 31 of these 38 patients. Pain was the most common symptom, varying in type but being rather uniformly severe. The clinical findings were variable, but a palpable tumor was found in 42 of the 73 patients, and roentgenograms revealed erosion of the vertebrae in 18 of the 24 so studied. Two thirds of the patients were under 45. The majority were Negro men who did hard labor, and 39 were proved to have syphilis.

The Incidence of Cardiovascular Syphilis.—Sprague and White,[102] in a general consideration of the prophylaxis of heart disease, forecast that syphilitic heart disease may soon be wiped out by virtue of the adequate treatment of early syphilis, and in this connection present some extremely interesting figures. In the ten years from 1900 through 1909 aortic aneurysm was the diagnosis for 113 of the 51,875 patients admitted to the Massachusetts General Hospital, an incidence of approximately 0.2 per cent. In the decade which ended in 1934, however, in spite of better methods of diagnosis, the diagnosis of aortic aneurysm was made for only 61 of the 75,184 patients admitted, an incidence of 0.08 per cent.

Maher, Sittler and Elliott [103] analyzed the data on 1,000 private patients with heart disease, all living in the vicinity of Chicago. In 97, or 9.7 per cent, the heart disease was due to syphilis.

General Considerations.—In an important communication Cormia [104] reports a review of all of the cases of cardiovascular syphilis in which

101. Kampmeier, R. H.: Aneurysm of the Abdominal Aorta: A Study of Seventy-Three Cases, Am. J. M. Sc. **192**:97 (July) 1936.

102. Sprague, H. B., and White, P. D.: The Etiology of Heart Disease with Special Reference to the Present Status of the Prevention of Heart Disease, J. A. M. A. **105**:1391 (Nov. 2) 1935.

103. Maher, C. C.; Sittler, W. W., and Elliott, R. A.: Heart Disease in the Chicago Area, J. A. M. A. **105**:263 (July 27) 1935.

104. Cormia, F. E.: Cardiovascular Syphilis: A Necropsy Survey, Canad. M. A. J. **33**:613 (Dec.) 1935.

autopsy was performed in the Royal Victoria Hospital in the thirty-five years ending in 1934. There were 199 such cases, representing 2.68 per cent of the total number of autopsies. By a tabulation of incidence for five year periods the author shows that aside from a peak in the period 1910 to 1914, the incidence of cardiovascular syphilis has not materially changed but the incidence of myocarditis and that of coronary artery disease are increasing. Not one of these patients had had adequate treatment for early syphilis.

There were 156 men and 43 women. The common age of death was 50 years. Fifty-eight patients had other lesions of syphilis; in these cardiovascular syphilis was the cause of death in all but 6, 3 of whom had dementia paralytica and 1 had tabes dorsalis. In 34 of the 44 instances of aortitis there had been no symptoms, which is not surprising, since all of those with outspoken dilatation of the aorta were considered as having fusiform aneurysm. The 10 with symptoms had lived on the average only a year and two months after the symptoms developed. The span of life from the development of symptoms until death had been three years for patients with aneurysm, one year and ten months for those with aortic regurgitation and two years for those with both conditions. There were 35 instances of syphilitic involvement of the coronary arteries, either at their ostia or in the distal trunks; one third of the 33 patients with aortic regurgitation and 18 of the 40 with both aortic regurgitation and aneurysm manifested this abnormality. However, only 1 of the 60 patients with aneurysm alone also had syphilitic disease of the coronary arteries, although in 18 arteriosclerotic changes were noted. There were 20 patients in whom syphilis of the myocardium independent of coronary disease was suspected; it seemed definite in 14 and questionable in 6.

Bourne,[105] in a general consideration of cardiac pain, says:

> Patients with aortic syphilis suffer from three types of pain, excluding that produced by a definite aneurysm—these are: angina of effort, spasmodic angina, and nocturnal pain. The angina of effort is identical in every particular with that already described, but it is found typically in a patient who has no signs of hyperpiesis or arteriosclerosis, and in whom, if there is no aortic incompetence, the heart is not enlarged. In patients with a syphilitic aortic regurgitation, in adition to angina of effort, a spasmodic angina is sometimes found. This is symptomatically identical with spasmodic angina in nonsyphilitic cases. A nocturnal pain, recognized sometimes by the patients as being of a cardiac nature, is not uncommon in syphilitic aortitis. It is generally central, and may be felt in front under the sternum, or may be referred more to the back.

105. Bourne, G.: The Symptomatology of Cardiac Pain, Brit. M. J. **1**:1109 (June 1) 1935.

The Treatment of Cardiovascular Syphilis.—Employing the method of study used by Moore, Danglade and Reisinger,[106] Stratton[107] studied the effects of treatment or its lack on the life span of 80 patients with aortic insufficiency or aneurysm and corroborated in every respect the earlier observations. Cole and Usilton,[108] writing for the Cooperative Clinical group, present a series of three papers which are based on a study of the material collected and analyzed by the group.

Padget and Moore[109] seized the opportunity to resurvey the group of patients reported on by Moore, Danglade and Reisinger[106] after an additional three years of observation. Using a simpler method of analysis than in the previous study and dealing only with the duration of life in reference to antisyphilitic treatment, these authors consider a group of 161 cases of aortic regurgitation or saccular aortic aneurysm in which the mean potential period of observation was ten and three-fourth years and in which no living patient had been under observation for less than five and one-half years. One third of the patients had died in less than a year of observation and so were eliminated from a consideration of the therapeutic results.

Such a study is not complete, say the authors, until all the patients are dead, but in the meantime examination of the mortality rates for various groups affords valuable information. "The mortality rate for the poorly treated group was 1.37 times that of the well treated group in patients with aneurysm; 2.52 times as great in those with aortic insufficiency; and 2.02 times as great for the group as a whole," with an even more striking contrast when deaths due to cardiovascular syphilis and deaths due to other diseases or to causes unknown are considered. In the 70 patients of the group considered who are dead "the duration of life from onset of symptoms . . . was 1.7 times as great in the well treated as in the poorly treated patients for the whole group; 1.71 times as great in those with aneurysm; and 1.37 times as great in the patients with aortic insufficiency . . ." The latter figure was not claimed to have certain statistical significance, but all others were.

106. Moore, J. E.; Danglade, J. H., and Reisinger, J. E.: The Treatment of Cardiovascular Syphilis, Arch. Int. Med. **49**:879 (June) 1932.

107. Stratton, E. K.: The Treatment of Cardiovascular Syphilis: A Study of the Duration of Life in Eighty Treated and Untreated Patients with Aortic Aneurysm and Aortic Regurgitation, Arch. Int. Med. **56**:773 (Oct.) 1935.

108. Cole, H. N., and Usilton, L. J.: Cooperative Clinical Studies in the Treatment of Syphilis: Cardiovascular Syphilis; I. Uncomplicated Syphilitic Aortitis: Its Symptomatology, Diagnosis, Progression and Treatment, Arch. Int. Med. **57**: 893 (May) 1936; II. Syphilitic Aortic Regurgitation: Its Treatment and Outcome, ibid. **57**:910 (May) 1936; III. Aneurysm: Its Symptomatology, Diagnosis, Treatment and Outcome, ibid. **57**:919 (May) 1936.

109. Padget, P., and Moore, J. E.: The Results of Treatment in Cardiovascular Syphilis: A Report of Three Years' Additional Observation, Am. Heart J. **10**:1017 (Dec.) 1935.

The authors conclude that "properly directed antisyphilitic therapy results in a prolongation of life in two thirds of the patients with saccular aortic aneurysm or syphilitic aortic insufficiency. The remaining third come under observation with an initially bad prognosis, and do not survive sufficiently long for proper therapy to be administered."

NEUROSYPHILIS

Statistics.—Merriman [110] estimates that neurosyphilis occasioned 11.3 per cent of all admissions to civil state hospitals during the year ending in June 1933, and he restates the estimate that neurosyphilis cost the state of New York alone $13,500,000 during the year 1931.

In an analysis of the outcome in patients with dementia paralytica Derby [111] reports on 1,475 consecutive admissions to a state hospital during the fifteen year period from 1917 to 1931. Malaria therapy was adopted in 1924 and tryparsamide the following year. A contrast is presented: The patients who received no treatment lived for an average of one and a third years after admission to the hospital; those who were treated by all means other than malaria lived for just more than three years, but the average survival of the patients who received chemotherapy and malaria treatment was five and three-fourth years.

The Genesis of Neurosyphilis.—In a lengthy review of the evidence regarding habitus and constitutional make-up as factors influencing the development of neurosyphilis, Meggendorfer [112] concludes that he agrees with most writers since Paracelsus that in a given subject infection with syphilis takes a form which is determined by the host but that there is as yet no evidence from which to determine the constitutional factors that are responsible.

Kemp and Menninger,[113] in examining the records of 1,500 patients admitted consecutively to a syphilis clinic, found 265 patients with neurosyphilis in whom the duration of infection and the amount of treatment for early syphilis could be accurately determined. From an analysis of this material they conclude that inadequate treatment for early syphilis does not increase the later incidence of neurosyphilis but does operate materially to shorten the incubation period. A similar conclusion is reported by Hall.[114]

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110. Merriman, W. E.: Syphilis and Mental Disease, J. Social Hyg. **21**:164 (April) 1935.

111. Derby, I. M.: Life Expectancy in General Paresis, Psychiatric Quart. **9**: 458 (July) 1935.

112. Meggendorfer, F.: Die Rolle der Konstitution bei der Spätlues des Nervensystems, Deutsche Ztschr. f. Nervenh. **139**:157 and 191, 1936.

113. Kemp, J. E., and Menninger, W. C.: The Influence of Inadequate Treatment of Early Syphilis on the Incidence and Incubation Period of Neurosyphilis, Bull. Johns Hopkins Hosp. **58**:24 (Jan.) 1936.

114. Hall, T. B.: The Influence of Early Therapy on the Incubation Period of Syphilis, South. M. J. **28**:631 (July) 1935.

Beringer [115] comments on the Russian-German expedition to Buriat-Mongolia. In this isolated Soviet republic the incidence of syphilis is high (25 to 50 per cent), and the disease is not treated. This expedition was organized to determine the form which syphilis takes when not influenced by treatment. Unfortunately, conditions were such that careful statistical surveys could not be made, but, according to this author, neurosyphilis was found to have approximately the same incidence as in European countries, indicating that neither a primitive racial stock nor the absence of antisyphilitic treatment protects against its development.

Disturbance of Carbohydrate Metabolism in Neurosyphilis.—There were many suggestions in the earlier literature that syphilis was an important cause of diabetes, and in the recent past all investigators have recognized the fact that since syphilis and diabetes are both not uncommon diseases their coexistence should be expected. Properly directed studies have shown that there is no evidence to indicate that the development of clinically typical diabetes mellitus in a patient with syphilis necessitates the assumption of an etiologic relationship. Blackford and Venable,[116] however, describe 2 patients, neither of whom was completely studied, but in both of whom glycosuria appeared only during convulsions associated with "paretic neurosyphilis." The authors suggest that the glycosuria may have resulted from syphilitic disease of the basal nuclei and not from true diabetes. Schube,[117] reasoning that since the lesions of parenchymatous neurosyphilis are widely distributed throughout the nervous system, a piqûre phenomenon might sometimes occur, examined the level of the blood sugar during fasting in 211 patients with various forms of neurosyphilis, with negative results.

The Treatment of Neurosyphilis.—Although Lorenz [118] begins a general discussion of the treatment of neurosyphilis with the statement that "the treatment of neurosyphilis is largely a problem for the general practitioner," such is not the usual opinion, and the treatment of neurosyphilis in most part remains properly concentrated in the hands of the experienced few. Except for one paper on the use of acetarsone in the therapy of neurosyphilis, recent contributions to the subject have dealt entirely with induced fever. Here, authors have discussed the

115. Beringer, K.: Die syphilidogenen Erkrankungen des Nervensystems bei den Burjato-Mongolen, Arch. f. Psychiat. **103**:359, 1935.

116. Blackford, L. M., and Venable, J. H.: Hyperglycemia and Paresis, New England J. Med. **214**:140 (Jan. 23) 1936.

117. Schube, P. G.: The Blood Sugar in Uncomplicated and Untreated Neurosyphilis, J. Lab. & Clin. Med. **21**:404 (Jan.) 1936.

118. Lorenz, W. F.: The Treatment of Neurosyphilis, South. M. J. **29**:74 (Jan.) 1936.

indications for fever therapy, the choice of method, complications to be feared, the mode of action and the results to be obtained.

Acetarsone in the Treatment of Neurosyphilis.—Sézary and Barbé [119] report that they have used acetarsone for the treatment of dementia paralytica since 1921 with "cure," [120] improvement, arrest and failure, respectively, in one fourth of their patients. Unfortunately, the number of patients they have so treated is not stated.

Indications for Fever Therapy.—Menzies [121] emphasizes that fever therapy should not be limited to patients with dementia paralytica but that patients with other forms of neurosyphilis, especially those with tabes dorsalis, may be much benefited by it. The pains of tabes, he says, respond particularly well to fever therapy, although, of course, some disability usually persists.

Doan and Hargraves [122] approach the question from the point of view of the cellular pathologist. It is impossible, they say, rationally to determine the uses and limitations of fever therapy until the fundamental mechanism which underlies each disease process has been discovered, the influence of fever on the various physiologic and pathologic functions of the body has been established and the effect of the latter on the former has been carefully calculated.

The Choice of Method for Fever Therapy.—With the great popularization of mechanical methods of elevating the temperature of the human body, there has been a rather generalized, often thoughtless rush to utilize these methods for the treatment of neurosyphilis. The results of the experiences previously summarized [1] seemed to indicate the superiority of malaria for the treatment of neurosyphilis, but comparisons of strictly parallel series were lacking. Epstein, Solomon and Kopp [123] now supply that defect. From a careful survey of the literature and a comparison of the results which they obtained by the diathermy fever treatment of 33 patients with the outcome observed in a similar group they had treated with malaria, these authors conclude: "In our hands, fever produced by diathermy has some value in the treatment of dementia paralytica but it is not so good as malaria therapy. Likewise, in a review of the literature it fails to prove to be a valuable substitute for malaria, although from our studies it appears to have distinct therapeutic value."

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119. Sézary, A., and Barbé, A.: The Treatment of General Paresis with Stovarsol, Internat. Clin. **1**:130 (March) 1936.

120. The quotation marks are ours.

121. Menzies, E. C.: Rationale of Malarial Therapy in Cerebrospinal Syphilis, Canad. M. A. J. **33**:504 (Nov.) 1935.

122. Doan, C. A., and Hargraves, M. M.: Fever Therapy: Its Indications and Its Limitations, Hospitals **10**:88 (June) 1936.

123. Epstein, S. H.; Solomon, H. C., and Kopp, I.: Dementia Paralytica: Results of Treatment with Diathermy Fever, J. A. M. A. **106**:1527 (May 2) 1936.

Desjardins,[124] while recommending that mechanically induced fever should supplant malaria for reasons of safety and convenience, says:

> These tests appear to have shown that in dementia paralytica, tabes dorsalis and syphilis of the nervous system generally, the results obtained by physical methods appear to be about the same as those obtained by malarial inoculation.

He adds, however:

> The evidence is not absolutely conclusive because the number of patients . . . is not yet sufficiently large . . . our own experience . . . has been too limited.

In the selection of the physical method to be employed, Desjardins, Stuhler and Popp[125] note the tendency to employ the "hot box" rather than electrical methods for the elevation of body temperature and describe in detail the Kettering hypertherm, which is an excellent example of this type of apparatus.

In almost all the treatment of neurosyphilis with malaria the tertian variety has been used, and in all the large series of cases in the literature this variety has been employed. It has been common experience, however, that many Negroes are spontaneously immune to tertian malaria, and in several centers it has become the practice regularly to treat patients of this race with quartan malaria, without, however, there being indisputable evidence that the end-results were as good. This needed evidence is now slowly accumulating, and Branche[126] reports on a series of 36 Negroes with dementia paralytica treated with quartan malaria in which the primary clinical results were excellent; his report was made too soon after the treatment was given to allow an evaluation of the final results. An interesting, although probably not practicable, suggestion is made by van Rooyen and Pile,[127] who treated 12 patients with dementia paralytica with ape malaria (Plasmodium Knowlesi), with apparent good results.

Untoward Results from Therapeutic Malaria.—Shaughnessy[128] notes that although Great Britain and Denmark have regulations which require that a patient be screened during the course of inoculation malaria, no such regulations exist in the United States. In his opinion this is reprehensible, because to him the evidence is imperfect that the sexual

124. Desjardins, A. U.: Fever Therapy, Arch. Phys. Therapy **17**:206 (April) 1936.

125. Desjardins, A. U.; Stuhler, L. G., and Popp, W. C.: Fever Therapy for Gonococcic Infections: II, J. A. M. A. **106**:690 (Feb. 29) 1936.

126. Branche, G. C.: Therapeutic Quartan Malaria in the Treatment of Neurosyphilis Among Negroes, J. Nerv. & Ment. Dis. **83**:177 (Feb.) 1936.

127. van Rooyen, C. E., and Pile, G. R.: Observations on Infection by Plasmodium Knowlesi (Ape Malaria) in the Treatment of General Paralysis of the Insane, Brit. M. J. **2**:662 (Oct. 12) 1935.

128. Shaughnessy, H. J.: Artificially Induced Malaria as a Public Health Hazard, Illinois M. J. **69**:147 (Feb.) 1936.

cycle of the parasite, and therefore the transmissibility of the disease by mosquitoes, disappears on repeated man to man passage. In support of this view he mentions a group of 11 patients, 6 hospital employees and 2 nearby residents in whom atypical malaria developed while the treatment of patients with malaria inoculata was being carried on in the hospital. Unfortunately for the substantiation of his contention, it is possible that the strain of therapeutic malaria employed had been freshly isolated.

Petersen [129] reports that in 14 of 261 patients who were treated with tertian malaria the parasite was found in the blood as long as one hundred and fifty weeks after the cessation of fever and after the patients had received an average of 44 Gm. of quinine. Nine other patients and 2 patients seen after malaria therapy had been given elsewhere, representing infection with four different strains of Plasmodium vivax, suffered definite clinical relapse. The author does not comment on whether the strains were freshly isolated or not or whether it is possible that the drug used in the treatment of the original infection might have been substandard.

Milbradt [130] saw no serious damage to the liver develop in over 1,000 cases of inoculation malaria. There was no swelling of the liver except when icterus was present and seldom then. In 25 cases tests of hepatic function were made before and after treatment with malaria and in the few patients in whom some damage was detected immediately after the fever was terminated the results of later tests were within the normal range.

The Mode of Action of Malaria.—Wagner-Jauregg [131] reviews the available evidence and concludes that malaria is superior to other means of inducing fever for the treatment of neurosyphilis.

The mode of action of fever on the nervous system has been, he says, the subject of much speculation; few facts have been obtained. Hypotheses have been advanced attempting to explain the observed facts on the basis of some change wrought in the reticulo-endothelial system by fever; by assuming a change from an anergic to an allergic state or an increase in the "reactivity" of the body, and by assigning a fundamental causal relationship to the observed increase in the opsonic index and the greater rate of antibody formation. These and other speculations may be true or partly so, but there is evidence that direct action occurs within the nervous system; there are characteristic changes

129. Petersen, M. C.: Recurrence of Inoculation Malaria, J. A. M. A. **106:** 775 (March 7) 1936.

130. Milbradt, W.: Zur Frage der Leberschädigung nach Impfmalaria, Dermat. Wchnschr. **101:**1182 (Sept. 21) 1935.

131. Wagner-Jauregg, J.: Fever Therapy: Its Rationale in Diseases of the Nervous System, Edinburgh M. J. **43:**1 (Jan.) 1936.

in the cerebrospinal fluid during malaria, anatomic evidence of focal reaction is repeatedly observed, and patients with "preparetic neurosyphilis" frequently show psychic disturbances while undergoing treatment with malaria. Doan and Hargraves [122] report observations on the blood picture and cellular reactions of man and rabbits during induced fever but are as yet unable to interpret their findings in terms of fundamental cellular reaction. Paulian and Tanasescu [132] believe the fundamental beneficence of malaria is the alteration of the hemato-encephalic barrier so as to allow greater penetration of the neuraxis by treatment given after the fever has been induced. In supporting this contention they state that whereas normally the trivalent arsenicals penetrate to the cerebrospinal fluid only in traces, in patients who are given malaria treatment there may be as much as 2 mg. of arsenic per liter of cerebrospinal fluid four hours after the injection of 0.3 Gm. of neoarsphenamine.

The Results of Treatment of Neurosyphilis.—In an article of extreme interest and great value Cheney [133] analyzes the data relating to 5,229 patients with dementia paralytica who were treated in the hospitals of the New York State Department of Mental Hygiene. Two hundred and forty-nine patients were treated with tryparsamide; 20 per cent of these gained a full remission and an additional 25 per cent were improved. There were 410 patients treated with malaria alone or in conjunction only with a trivalent arsenical and heavy metal; 18 per cent of these gained a full remission, and an additional 32 per cent were improved. Finally, 2,507 patients received, in addition to other therapy, both malaria and tryparsamide; 17 per cent of these gained remission, and an additional 38 per cent were improved. Only 15 per cent of the group treated by both methods have died, however, while 31 per cent of those treated with tryparsamide alone and 29 per cent of those who received only malarial therapy are dead. The combined therapy, then, is followed by no more complete remissions than either method alone. It is, however, followed by a somewhat higher percentage of improvement than either malaria or tryparsamide alone but allows to survive, unimproved, twice as many patients as either of the other methods of therapy. Levin [134] treated 100 patients with dementia paralytica with malaria alone and a similar

132. Paulian, D., and Tanasescu, G.: Récherches sur la perméabilité aux novarsenobenzols de la barrière hémato-méningo-encéphalitique dans la paralysie générale avant et après la malariathérapie, Bull. Acad. de méd., Paris **113**:850 (June 11) 1935.

133. Cheney, C. O.: Clinical Data on General Paresis, Psychiatric Quart. **9**: 467 (July) 1935.

134. Levin, H. L.: Treatment of General Paresis: Comparative Results, Psychiatric Quart. **9**:636 (Oct.) 1935.

group with malaria followed by tryparsamide. He found exactly the same state of affairs as did Cheney in the patients who had only one or two courses of tryparsamide after malaria treatment but discovered that the incidence of improvement was greatly increased by prolonging the tryparsamide treatment to 30 or 40 or more injections.

Solomon and Epstein [135] present a small series of cases the study of which suggests that therapy with both malaria and tryparsamide is more effective if the malaria is preceded by a considerable number of injections of tryparsamide.

Ridgway [136] and Buduls [137] report on a series of malaria-treated patients with dementia paralytica in which the results were in keeping with previous experiences.[1]

The Fever Therapy of Ocular Syphilis.—Clark [138] presents a most encouraging report of the results of treatment by fever therapy of 12 patients with advanced primary atrophy of the optic nerve. Inoculation with malaria, which he considers superior to other methods, was employed for all but 1 patient (she was refractory to inoculation). Four gained no benefit, and the process advanced to the stage of complete blindness, but in 8 the process was arrested, and some gained a little improvement in visual acuity or the defects in the visual fields were reduced.

Culler and Simpson,[139] in a bizarre grouping of syphilitic conditions about the eye which are unrelated in their pathogenesis, discuss the results which were obtained by a total of fifty hours of fever with temperatures above 105 F. induced in a Kettering hypertherm. Four patients with extra-ocular palsy were not improved, but 11 patients with previously refractory or relapsing interstitial keratitis were improved, and in 10 patients with exudative uveitis resolution was dramatically prompt and complete. In 14 patients with optic neuritis or neuroretinitis and in 7 with choroiditis the acute process subsided after fever therapy, but there were the expected residua. Sixteen patients with (presumably primary) atrophy of the optic nerve were so treated. It is reported that no change was obtained, but it is not possible from the report to determine whether atrophy continued or whether the progress of the process was stopped.

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135. Solomon, H. C., and Epstein, S. H.: General Paresis: Treatment by Tryparsamide-Induced Fever Sequence, Am. J. Syph., Gonor. & Ven. Dis. **20**:281 (May) 1936.

136. Ridgway, R. F. L.: Malaria Treatment of Paresis, Pennsylvania M. J. **39**:329 (Feb.) 1936.

137. Buduls, H.: Allg. Ztschr. f. Psychiat. **104**:168 (Feb. 3) 1936.

138. Clark, C. P.: Rôle of Malaria in Control of Atrophy of the Optic Nerve Due to Syphilis, Arch. Ophth. **15**:250 (Feb.) 1936.

139. Culler, A. M., and Simpson, W. M.: Artificial Fever Therapy in Cases of Ocular Syphilis, Arch. Ophth. **15**:624 (April) 1936.

Clinical Phenomena of Neurosyphilis.—A group headed by Langworthy [140] has been systematically studying the tone and function of the bladder and the pathways involved in their control in man and in experimental animals. For this purpose they have developed a technic for kymographic recording of the response of the bladder to successively introduced increments of fluid (in man usually 50 cc.). Records so obtained graphically present evidence of the conditions of vesical dynamics. They emphasize that changes observed are due to the anatomic location of a lesion in the central nervous system and not to its etiology. Tabes dorsalis, other diseases which involve the posterior roots, experimental section of the second, third and fourth posterior sacral roots and lesions of certain cerebellar pathways produce similar pictures. The bladder has a large capacity, a low resting pressure and poor power as measured by the height to which pressure may be elevated and sustained by a voluntary effort to micturate. It shows little response to stretching and few or no spontaneous contractions. These abnormalities "are dependent on a loss of perception of bladder distention due to injury of the sensory nerve fibers—made worse by the stretching of the wall." Their review of the histories of 278 patients with tabes dorsalis revealed that 140 of them had complained of urinary symptoms. Incontinence, which was nocturnal in 22, was noted in 83 cases; 71 patients had experienced hestitancy, and 19 had suffered from acute urinary retention. Almost all the group had had lightning pains at some time, but vesical crises were infrequent.

Binet and Parrot [141] emphasize that in patients suffering the constant vomiting of tabetic gastric crises, the loss of chlorides may soon overshadow other elements in the pathogenesis of the clinical condition, and proper therapy includes replacement of the lost chlorides when necessary.

While we have found it necessary to eliminate from consideration here discussions of small series or individual case reports which relate to treatment or the well recognized reactions therefrom, we have encountered a few descriptions of unusual clinical conditions produced or probably produced by syphilis which we think should be mentioned.

Uchimura and Akimoto [142] present the case of a Japanese housewife with syphilis in whom pseudohypertrophic muscular dystrophy and a

140. Dees, J. E., and Langworthy, O. R.: Experimental Study of Bladder Disturbances Analogous to Those of Tabes Dorsalis, J. Urol. **34**:359 (Nov.) 1935. Langworthy, O. R.; Lewis, L. G.; Dees, J. E., and Hesser, F. H.: Clinical Study of the Control of the Bladder by the Central Nervous System, Bull. Johns Hopkins Hosp. **58**:89 (Feb.) 1936.

141. Binet, L., and Parrot, J.: La crise gastrique du tabes; crise hypochlorémiante, Presse méd. **43**:2001 (Dec. 11) 1935.

142. Uchimura, Y., and Akimoto, H.: Ueber die Wernickesche Polioencephalitis als Teilerkrankung der vasculären Hirnlues, Ztschr. f. d. ges. Neurol. u. Psychiat. **152**:685 (May) 1935.

nondescript psychosis of the manic type developed. The complement fixation test of the cerebrospinal fluid gave a negative reaction, but there was an excess of globulin, and the colloidal curve was abnormal. Death ensued, and necropsy revealed extensive (supposedly syphilitic) endarteritis, which had produced in the brain and brain stem changes similar to those described as Wernicke's polioencephalitis.

Karnosh and Connor [143] discuss the infrequency with which neurosyphilis attacks the basal nuclei and point out that pseudobulbar palsy with pathologic grimacing as a result of neurosyphilis is rare. They have observed 2 cases, however, which are reported in full.

Winkelman [144] in a monographic series of articles gives a detailed discussion of syphilis of the spinal cord, with a complete bibliography. The article does not lend itself to summary here.

THE RELATIONSHIP BETWEEN SYPHILIS AND OTHER DISEASES

Syphilis and Tuberculosis.—Guild and Nelson [145] investigated current practice in the diagnosis and treatment of coexistent syphilis and tuberculosis by sending questionnaires to representative tuberculosis sanatoriums. Replies were received from 67, representing experience with more than 25,000 patients with tuberculosis during 1933. It was found that the hospitals in which a serologic test for syphilis was made only on suspicion or request discovered only one-fourth as many cases of syphilis as did the otherwise strictly comparable group of institutions in which a serologic test for syphilis was made as a routine. This can mean only that the former sanatoriums are missing 3 of 4 cases of syphilis. Wide differences of opinion in regard to antisyphilitic treatment in the presence of pulmonary tuberculosis were encountered, and there was no uniformity of practice in the different institutions. As the authors wryly point out, about the only discernible common factor was the tendency to give treatment once a week. In contrast to this, Guild and Nelson gained the impression that in a given institution, antisyphilitic treatment tended to be standardized and that if any treatment was given it was given in only one way, irrespective of the type of tuberculosis coexistent.

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143. Karnosh, L. J., and Connor, W. H.: Syphilitic Pseudobulbar Palsy with Compulsive Weeping, Am. J. Syph., Gonor. & Ven. Dis. **20**:115 (March) 1936.

144. Winkelman, N. W.: Syphilis of the Spinal Cord, Am. J. Syph. & Neurol. **19**:378 (July) 1935; Am. J. Syph., Gonor. & Ven. Dis. **20**:62 (Jan.); 421 (June) 1936.

145. Guild, C. St. C., and Nelson, M.: The Problem of Coexisting Syphilis and Tuberculosis in Light of Current Opinion and Practice, Am. Rev. Tuberc. **33**:31 (Jan.) 1936.

In a consideration of the interrelationships of tuberculosis, syphilis and antisyphilitic treatment Padget and Moore [146] point out that most of the studies of these interrelationships between the two diseases have been made from the point of view of those interested primarily in tuberculosis and that there is no uniformity of recorded opinion regarding the incidence of coexistence of the two diseases (i. e., the tendency of one to predispose to the other), the effect of either one on the course of the other or the influence of antisyphilitic therapy on tuberculosis.

Examination of the available information revealed that no study of the incidence of coexistence of the two diseases, including that from their own material, provides a basis for valid conclusions. In the opinion of these authors the question can never be solved by retrospective study but may be approached only by the preplanned observation of a large group of patients over a long period of time. The basic scheme for such a study is outlined.

It is noted that there are numerous clinical impressions that active tuberculosis favorably modifies the course of syphilitic infection, but the authors emphasize the lack of definitive information in this regard and point out that this question may be solved, if at all, only by animal experimentation, the applications of which are limited in this field. Contrarily several carefully studied series of cases document the consensus of competent physicians that untreated syphilis adversely affects the course of tuberculous infection.

The important point, however, is the effect on the patient of the introduction of antisyphilitic treatment into the picture of coexistent syphilis and tuberculosis. Reports from various hospitals for tuberculous patients indicate that mild antisyphilitic treatment reduces the mortality from tuberculosis and results in clinical improvement of the pulmonary infection of patients suffering from both diseases, as contrasted with appropriate control groups. This type of treatment, however, is totally inadequate for certain forms of syphilis (e. g., dementia paralytica) which are more certainly fatal than even exudative pulmonary tuberculosis, and it is emphasized that the currently adopted attitude that tuberculosis is the more important disease when it coexists with syphilis is not necessarily correct.

Finally, the authors report a series of 15 cases in all of which intensive antisyphilitic treatment had been closely followed by and probably had occasioned the fulminating development of previously unrecognized (and they believe unrecognizable) pulmonary tuberculosis.

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146. Padget, P., and Moore, J. E.: The Interrelationships of Tuberculosis, Syphilis and Antisyphilitic Treatment, Am. Rev. Tuberc. **33**:10 (Jan.) 1936.

Collating this experience, they emphasize that the treatment of coexistent tuberculosis and syphilis must not be regarded as a routine matter in any instance in regard to either disease but must be determined by close cooperation between physicians expert in these fields.

Syphilis and Primary Glaucoma.—Beckh [147] investigated this subject and says:

> A study was made of the incidence of syphilis in a group of 355 consecutive public ward patients with primary glaucoma . . . to establish if there is any basis, on clinical grounds, for the entity "primary syphilitic glaucoma," . . . . . No relationship between syphilis and primary glaucoma was suggested by a comparative study, with various control groups, from the point of view of incidence, age of onset, and response to specific therapy. A review of the manifestations of syphilis in patients with syphilis and primary glaucoma showed the luetic process to be latent in 82 per cent of the cases. A study of 11 cases of buphthalmos did not point to an etiological connection with syphilis.

Late Effects of Adequate Antisyphilitic Therapy.—Hall [148] studied the mortality figures of insurance companies for patients who had had syphilis and sufficiently adequate treatment therefor to be granted life insurance subsequently and discovered an apparent tendency to prematurely early death in these patients from other diseases, notably tuberculosis and cancer. He concludes:

> If further investigation and experience should prove the validity of the impressions and suppositions engendered by such a study as the present one, our forewarning will arm us with at least one potent weapon: the recognition of the cured syphilitic's diminished resistance to certain diseases in particular. If, by virtue of his past or present but latent disease, or by virtue of the extra load of antisyphilitic treatment he has borne, or both, he is recognized as probably being particularly susceptible to pulmonary tuberculosis, appendicitis, pneumonia and/or cancer, he can be given the advantage of all the appropriate knowledge which we have toward preventing and treating these conditions, when such susceptibilities are intelligently anticipated.

CONGENITAL SYPHILIS

The Diagnosis of Congenital Syphilis.—It has long been clear that the early institution of antisyphilitic therapy is as important in congenital as in acquired syphilis, but the former condition, on the average, presents a much more difficult problem for early diagnosis than the latter. Under the conditions of modern practice a woman with syphilis rarely bears a child without the fact she has syphilis being discovered and at least some treatment administered. This treatment, even though inadequate to protect the child from infection, almost always is enough to suppress the lesions, and the child is, at birth, apparently normal.

147. Beckh, W.: Syphilis and Primary Glaucoma, Am. J. Ophth. **18**:1129 (Dec.) 1935.

148. Hall, A. F.: Undertreatment Versus Overtreatment of Syphilis, J. Indiana M. A. **28**:586 (Nov.) 1935.

Serologic tests of blood from the cord are inadequate for early diagnosis, and the roentgenologically characteristic osseous lesions may not have developed, so valuable time may be lost before a diagnosis finally can be made. Impressed by this state of affairs, there have been a number of efforts to expedite the diagnosis. Ingraham [149] describes in detail the technic for dark field examination of material from the wall of the umbilical vein. If spirochetes are demonstrated the diagnosis of congenital syphilis is made within an hour of birth, but failure to find these organisms has no value in excluding infection of the child. Ingraham made a diagnosis of congenital syphilis by this method in more than a third of the instances in which the child later was proved by the more usual methods to be infected. Parmelee and Halpern,[150] in contrasting the efficiency of clinical, serologic and roentgenologic methods in the diagnosis of congenital syphilis, demonstrate the superiority of the latter, especially in children aged from 6 weeks to 3 months. Ingraham [151] verified the superiority of roentgenographic methods, and determined by the study of serial roentgenograms [152] that what he terms the "lag phase," i. e., the time which elapses between the infection with syphilis of the fetus and the appearance of roentgenologically demonstrable lesions, is five weeks for syphilitic osteochondritis and four months for syphilitic periostitis. He concludes, then, that a single roentgenogram taken when the infant is 6 weeks old should demonstrate the changes in practically every case, but that these may be found much sooner in many instances. He [153] finally sums up current opinion by contrasting the efficiency of the various diagnostic methods employed and emphasizes that a study of the ensemble is essential if the diagnosis is to be made at the earliest possible moment. Faber and Black [154] add a valuable observation. Under the term "Fildes' law" they restate Fildes' original observation thus: "Syphilitic reagin in the blood of the new-born infant is diagnostic not of syphilis in the infant but of syphilis in the mother." They observed, however, when they

149. Ingraham, N. R.: Congenital Syphilis: Diagnosis by Means of Dark-Field Examination of Scrapings from the Umbilical Vein, J. A. M. A. **105**:560 (Aug. 24) 1935.

150. Parmelee, A. H., and Halpern, L. J.: The Diagnosis of Congenital Syphilis, J. A. M. A. **105**:563 (Aug. 24) 1935.

151. Ingraham, N. R.: Roentgen-Positive Seronegative Infantile Congenital Syphilis, Am. J. Dis. Child. **50**:1444 (Dec.) 1935.

152. Ingraham, N. R.: The Lag Phase in Early Congenital Osseous Syphilis: A Roentgenographic Study, Am. J. M. Sc. **191**:819 (June) 1936.

153. Ingraham, N. R.: The Diagnosis of Infantile Congenital Syphilis During the Period of Doubt, Am. J. Syph. & Neurol. **19**:547 (Oct.) 1935.

154. Faber, H. K., and Black, W. C.: Quantitative Wassermann Tests in Diagnosis of Congenital Syphilis: Clinical Importance of Fildes' Law, Am. J. Dis. Child. **51**:1257 (June) 1936.

quantitated the serologic test for syphilis on blood from the cord that usually the blood from infants who subsequently were shown to have syphilis was positive in high titer, whereas that from the ones subsequently proved to be normal was of low titer. Furthermore, the titer in the latter group was found to decrease in serial tests, as little as a week apart, which was not true of the former. They suggest, therefore, that serial quantitative serologic tests for syphilis in an infant under suspicion may save much time in establishing a diagonsis.

Lesions of Congenital Syphilis.—Dorne and Zakon [155] call attention to the enlargement of the sternal end of one clavicle with consequent enlargement of the sternoclavicular articulation as a stigma of congenital syphilis. It was present in all of their group of 12 older children and adults with congenital syphilis. Döderlein [156] reports finding delay in the ossification of the petrous portion of the temporal bone in syphilitic fetuses, and Brown [157] found numerous intestinal lesions, which he describes as gummas but which were teeming with spirochetes (S. pallida), in a premature syphilitic infant who died an hour after birth. Reich [158] reports 5 cases of osteochondritis occurring in older (7 to 14 years) children with congenital syphilis. Since in the 4 who were treated for syphilis the osteochondritis promptly resolved, Reich considered it to be syphilitic in origin.

The Treatment of Congenital Syphilis.—Smith [159] presents detailed analyses of the entire experience of the pediatric department of the Johns Hopkins Hospital.

Acetarsone in the Treatment of Congenital Syphilis: Traisman [160] has now extended his series of children with congenital syphilis treated

155. Dorne, M., and Zakon, S. J.: Enlargement of One Sternoclavicular Articulation as a Valuable Clinical Sign of Late Prenatal (Congenital) Syphilis, Arch. Dermat. & Syph. **32**:602 (Oct.) 1935.

156. Döderlein, W.: Ueber den Einfluss der kongenitalen Lues auf die Verknöcherung der Labyrinthkapsel beim Neugeborenen, Arch. f. Ohren-, Nasen- u. Kehlkopfh. **140**:229 (Jan. 3) 1936.

157. Brown, A. F.: Intestinal Lesions in Congenital Syphilis, Arch. Path. **21**:251 (Feb.) 1936.

158. Reich, B.: Osteochondritis syphilitica bei Lues congenita tarda: Spezifische Erkrankungen der Epiphysenlinien bei älteren Kindern mit kongenitaler Spätlues; Beobachtungen an 5 Fällen, Deutsche Ztschr. f. Chir. **245**:437 (Sept.) 1935.

159. Smith, F. R., Jr.: Congenital Syphilis in Children: Results of Treatment in Five Hundred and Twenty-One Patients: I, Am. J. Syph. & Neurol. **19**:532 (Oct.) 1935; II, Am. J. Syph., Gonor. & Ven. Dis. **20**:45 (Jan.) 1936; Congenital Syphilis: The Results of Treatment in Children, J. A. M. A. **105**:409 (Aug. 10) 1935.

160. Traisman, A. S.: Further Observations on the Use of Acetarsone in the Treatment of Congenital Syphilis, J. Pediat. **7**:495 (Oct.) 1935.

with acetarsone to 65, and his period of observation to three years. The early promise given by the original results from acetarsone therapy has in his opinion been fulfilled, and Traisman concludes that it is the ideal drug for the oral treatment of congenital syphilis in the infant. Davidson and Birt,[161] from experience with 37 children, are equally enthusiastic.

Malaria Therapy: Wile and Hand[162] received replies to a questionnaire concerning 24 patients with juvenile dementia paralytica seen by them over a period of seven years. Half of the 10 who had not received treatment with malaria were dead, and the condition of the remainder was unchanged or worse. Two of 14 who received malaria therapy were improved, 2 were dead and the reports revealed the condition of the remainder to be unchanged or worse. Since those who received malaria treatment were in somewhat better condition when first seen than those in the other group, these authors believe that malaria is of little value in the treatment of juvenile dementia paralytica, and they conclude that to be effective malaria treatment of juvenile neurosyphilis must be given in the asymptomatic stage of the disease. Kidd,[163] who had used malaria in the treatment of a wide variety of forms of congenital syphilis with usually excellent results, is equally gloomy concerning the prognosis of clinically apparent juvenile neurosyphilis, with or without malaria therapy, but Palisa[164] reports complete or good remission in 10 (37 per cent) of 27 malaria-treated patients with juvenile dementia paralytica and slight remission in 5 others.

THIRD GENERATION SYPHILIS

It has long been known and has been a matter of considerable interest that the transmission of syphilis from parent to child seldom goes beyond the second generation. There have been those, indeed, to contend that third generation syphilis does not occur. Stokes,[165] in his discussion of the subject, says in the first edition of his textbook, "Personally I have yet to see a report which is beyond cavil," but in

161. Davidson, A. M., and Birt, A. R.: The Treatment of Congenital Syphilis with Stovarsol, Canad. M. A. J. **34**:33 (Jan.) 1936.

162. Wile, U. J., and Hand, E. A.: Juvenile Dementia Paralytica, with Especial Reference to Its Treatment with Malaria, J. A. M. A. **105**:566 (Aug. 24) 1935.

163. Kidd, R. A.: Malaria Treatment in Congenital Syphilis, Ohio State M. J. **32**:645 (July) 1936.

164. Palisa, C.: Zur Therapie und Prognose der juvenilen Paralyse, Wien. klin. Wchnschr. **48**:716 (May 18) 1935.

165. Stokes, J. H.: Modern Clinical Syphilology, Philadelphia, W. B. Saunders Company, 1926, p. 1054.

the second edition [166] he modifies this to read as follows: "However, no reasonable doubt, albeit the extreme rarity is conceded, exists of third generation syphilis." In the latter edition, he cites the Fournier-Finger criteria, which in his opinion it is necessary to fulfil in order to establish a diagnosis of third generation syphilis: 1. Acquired syphilis must be demonstrated in the grandmother. 2. The syphilis of the mother must be proved to be congenital, and the father must be healthy. 3. The third generation child must have indisputable congenital syphilis. 4. Manifestations must have appeared in both the second and the third generation soon after birth.

In this light there have been several interesting reports. Rosenbaum [167] observed 2 families and describes 4 children of the third generation with congenital syphilis with a background almost fulfilling the Fournier-Finger criteria, and the cases of Boardman [168] and Valentova [169] seem conclusive. Elliott [170] adds to the Fournier-Finger criteria the previously taken for granted requirement that the parentage of the child suspected of third generation syphilis must be certain. He adds another case report, which is not entirely conclusive.

SYPHILIS AND PREGNANCY

Cole [171] reports the results of the study of the 603 women in the material studied by the Cooperative Clinical Group who had, under observation, 922 pregnancies after their syphilitic infection, the final outcome of which was known for 607. The important conclusions are: 1. Congenital syphilis is essentially a preventable disease. 2. Its prevention depends on "the routine, early and repeated use" of a serologic test for syphilis in every pregnant woman. 3. Once the diagnosis of syphilis is made its prevention depends on intensive antisyphilitic treatment of the mother. 4. The pregnant woman tolerates antisyphilitic treatment well. 5. Therapy begun before the fifth month of pregnancy is more certain to protect the fetus than treatment begun later, but even a little treatment late in pregnancy greatly improves the chance that the child will be nonsyphilitic. 6. To insure that her child

166. Stokes, J. H.: Modern Clinical Syphilology, ed. 2, Philadelphia, W. B. Saunders Company, 1934, p. 1271.

167. Rosenbaum, H. A.: Third Generation Syphilis, J. Pediat. **7**:797 (Dec.) 1935.

168. Boardman, W. P.: Syphilis in the Third Generation, Arch. Dermat. & Syph. **32**:660 (Oct.) 1935.

169. Valentova, O.: Syphilis in 3 Generationen, abstr., Zentralbl. f. Haut- u. Geschlechtskr. **53**:205 (April 5) 1936.

170. Elliott, A.: Third-Generation Syphilis, Brit. M. J. **1**:1206 (June 13) 1936.

171. Cole, H., and others: Cooperative Clinical Studies in the Treatment of Syphilis: Syphilis in Pregnancy, J. A. M. A. **106**:464 (Feb. 8) 1936.

will be normal, every woman known to have had syphilis should be given antisyphilitic treatment throughout every pregnancy, irrespective of the clinical status or the results of serologic tests.

Exner,[172] employing the questionnaire method which is generally utilized by the American Social Hygiene Association for gathering information, attempted to determine current clinic and private patient practice directed toward the prophylaxis of congenital syphilis. For clinic practice he concludes that while progress in this regard is evident, there is still great need for earlier diagnosis and early adequate treatment and there is an urgent demand for a better follow-up of children born of mothers with syphilis, in order not only to determine the outcome for the child but also to allow evaluation of the results of antepartum antisyphilitic therapy. Private practitioners, however, still evince considerable reluctance toward employing serologic tests for syphilis as a routine in their practice, although half of those who replied to the questionnaire reported that they did so.

Syphilis of the Placenta.—It has already been emphasized that the early diagnosis of congenital syphilis depends on an evaluation of the ensemble, in which no small place has been given [153] to the histologic appearance of the placenta. The report from Montgomery,[173] therefore, is disturbing to the orthodox. This author, in a restudy of sections from a large number of placentas, concludes that while unquestionably the placenta can transmit S. pallida from mother to fetus, the organ itself is singularly resistant to syphilitic infection. The areas of placental fibrosis, which others have considered diagnostic of syphilis of the placenta, this author says are not a pathologic entity, and when present in great numbers in the placenta from a syphilitic premature stillbirth, are a phenomenon of the prematurity and not of syphilis.

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172. Exner, M. J.: Syphilis in Pregnancy: Report of a Study, J. A. M. A. **106**:488 (Feb. 8) 1936.

173. Montgomery, T. L.: Fibrosis of the Placenta: Its Significance in the Normal and in the Syphilitic Organ, Am. J. Obst. & Gynec. **31**:253 (Feb.) 1936.

Book Reviews

Medical Mycology: Fungous Diseases of Men and Other Mammals. By Carroll William Dodge. Price, $10. Pp. 900, with 142 illustrations. St. Louis: C. V. Mosby Company, 1935.

This comprehensive volume is the result of ten years of study and of collecting material in the field of mycology. The book has chapters dealing with the general morphology of fungi and their physiology, culture mediums, methods of isolation, microscopy and nomenclature. Then follow sixteen chapters dealing with specific groups of fungi according to the author's classification.

It must be granted at the outset that few, if indeed any, working in those fields of medicine in which mycologic lesions are likely to be encountered have even a working knowledge of this greatly jumbled-up subject. The thousands of species described and the various and numerous classifications proposed have made the subject a nightmare to all serious students. The author, although he has done a monumental piece of work, unfortunately has not clarified the field, and by giving an entirely new classification with many new names has left the reader in an unending labyrinth. It is also unfortunate that the title suggests the inclusion of material which is not to be found in the pages of the monograph, and the physician will have his curiosity by no means satisfied, there being practically no treatment of the medical side of mycology. In addition, numerous species of fungi which have no significance in medicine, as for example the dozens of species of Actinomyces, are discussed, yet strangely enough one finds neither in the index nor under the description of species any mention of Actinomyces hominis. If the author intended to include it under Actinomyces bovis, no indication of the fact is given.

The author has slipped many times into a curious and clearly incorrect error in nomenclature. When in placing a species in a different genus he has found the specific name preoccupied, he has correctly given the species a new name but has added "Dodge, n. sp." to the name. Clearly this is not correct, since the species still belongs to the original author. Examples of this error are unfortunately found in the name of the organism causing torula infection in man and also the one causing madura foot.

Undoubtedly the greatest contribution the author has made in this book is listing the hundreds, perhaps thousands, of references to the literature up to the end of the year 1933. These have all the earmarks of having been carefully compiled, yet the reviewer has found that the references are not readily available, first, because there is no author index and, second, because the references are collected at the end of each chapter. Since the author has used an entirely new classification, one is often in a quandary as to where to look for specific references; further, references are not keyed into the text.

All in all this volume represents a huge amount of work in an important and chaotic field. While the author has not produced a solution to the general problem and has certainly not filled the great need for a practical medical mycology, he has, so to speak, in the words of one who is not a mycologist, put us "on our way."

Undersøgelser over nogle metalsaltes indvirkning paa fagocytose. By Paul Mørch. Paper. Pp. 224, with 7 illustrations and 47 tables. Copenhagen: Nyt Nordisk Forlag, 1933.

The experimental work described in this dissertation was done at the University of Copenhagen and is fundamental, its immediate importance concerning chiefly

immunology and general physiology. The body of the text is in Danish, but a detailed summary in readable German is given on pages 210 to 219 and should be called to the attention of any one who wishes to attempt work in this difficult field, since some of the sources of error in the determinations of phagocytic activity are only beginning to be appreciated. The influence of the salts of thirty-nine metals on phagocytosis was studied. Thirty-three were found to possess optimum concentrations at which they stimulated phagocytosis. These optima lay distributed within wide limits (10^{-1} to 10^{-10} molar), and no relation was found between the position of the metallic element in the periodic table and its optimum concentration for phagocytosis. The stimulation in the case of calcium, zinc, manganese and nickel amounted (at the optimum) to from 200 to 250 per cent more than that in the controls. Antimony, arsenic, erbium, lead, palladium and selenium were never found to stimulate phagocytosis, and the maximum obtained for mercuric salts was only 100 per cent above that of the controls.

Lobar Pneumonia and Serum Therapy. By Frederick T. Lord, M.D., and Roderick Heffron, M.D. Price, $1. Pp. 91, with 11 illustrations. London: Oxford University Press, 1936.

Some five years ago the Commonwealth Fund financed a study of pneumonia in Massachusetts. This booklet summarizes in a clinical way the results of this work.

The volume is an engaging monograph, clearly written, well printed and illustrated with simple diagrams. One unfamiliar with technic learns how to type pneumonia sputum by the Newfeld method, how to test a patient for sensitivity to serum and how best to administer antipneumococcus serum in properly selected cases. One learns of the expected results of the modern treatment of pneumonia. In Massachusetts during the last five years, patients with pneumonia, infected with type I or type II Pneumococcus, whose condition was recognized early and who received serum as quickly as possible fared well, on the whole.

A book of this character, so convenient for physicians and medical students to read and so full of common ungarnished sense is almost certain to be universally popular. The Commonwealth Fund and the authors are to be congratulated for presenting the results of their complicated study of public health in such a simple and useful manner.

Immunology. By Noble P. Sherwood, M.D., Professor of Bacteriology, University of Kansas. Price, $6. Pp. 608, with 8 colored plates and 27 other illustrations. St. Louis: C. V. Mosby Company, 1935.

Sherwood states that this book was written for medical students and for other persons who have had training in pathogenic bacteriology or inorganic and organic chemistry and who are interested in the underlying principles involved in infection, resistance and diagnostic laboratory tests. It is a nicely arranged, clearly written book, giving plain descriptions of various technical procedures, and is well printed and well illustrated. It has three features which will have great appeal to students: At the end of each chapter is a carefully chosen bibliography referring to the topic under discussion and stimulating wider reading. Near the end of the book is an authors' index which, among other information, gives one a fair idea of the present leaders in the field of immunology. And, finally, there is an excellent subject index, so that any information, from the definition of ablastin to facts about zootoxins, is easily obtainable. On the whole, the book belongs to that attractive species which at once feels at home and is a useful member of the family in any library, on any reference shelf or in any laboratory.